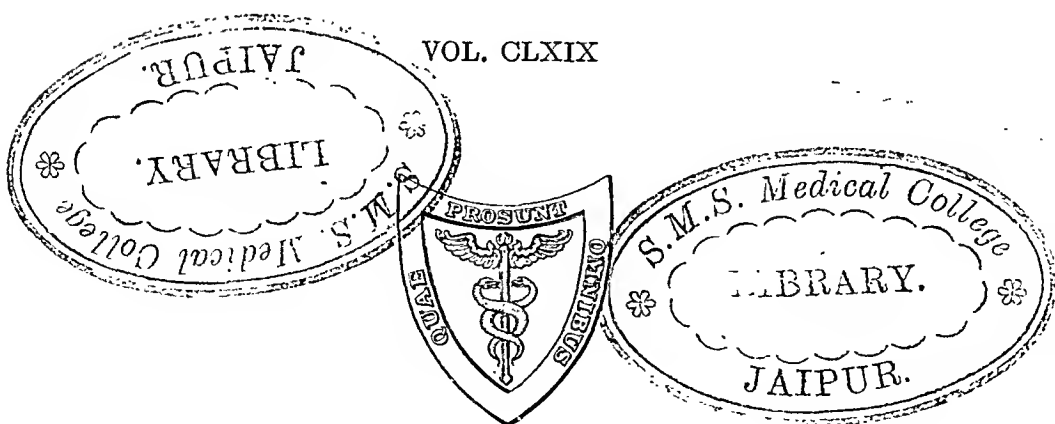


THE
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E. B. KRUMBHAAR, M.D.
EDITOR

RICHARD A. KERN, M.D.
ASSISTANT EDITOR

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THE
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ORIGINAL ARTICLES.

INJURIES TO THE MUSCULOSPIRAL NERVE.

BY W. RUSSELL MACAUSLAND, M.D.,

SURGEON-IN-CHIEF, ORTHOPEDIC DEPARTMENT, CARNEY HOSPITAL.

AND

ANDREW R. MACAUSLAND, M.D.,

ORTHOPEDIC SURGEON, CARNEY HOSPITAL, BOSTON, MASS.

THE musculospiral nerve is frequently involved in injuries of the upper extremity, due largely to the close approximation of the nerve to the shaft of the humerus in its middle third. von Busch,¹⁰ in 1863, was the first to describe the paralysis resulting from injury of the musculospiral nerve in fractures of the humerus. Since his discovery many attempts have been made to restore the anatomical continuity of the nerve. In the World War, operative procedures were used with an appreciable measure of success in cases of paralysis of the musculospiral nerve resulting from wounds or fractures.

Slight injuries to the musculospiral nerve are frequently overlooked, especially as the paralytic symptoms may disappear rapidly after reduction of the fracture. In some cases, however, paralysis follows injury to the nerve trunk, due to the original trauma or to subsequent pressure upon the nerve from bony callus or scar tissue. These injuries demand early recognition and treatment, for such damage unrecognized often leads to a serious loss of function.

Very little has appeared in American literature on this important subject. It is our purpose to review the literature, particularly that of foreign countries, and to present our personal experiences with several of the more severe types of these injuries.

Anatomy of the Nerve. The musculospiral nerve is the principal continuation of the posterior cord of the brachialis plexus, and the only branch prolonged into the arm. It arises behind the axillary vessels, turns backward with the superior profunda artery between the long and internal heads of the triceps, and runs beneath the external head of the muscle in the musculospiral groove of the humerus, to the outer side of the arm. It pierces the external intermuscular septum, and descends between the brachialis anticus and the supinator longus to the front of the external condyle, where it divides into the radial and posterior interosseous nerves. The radial is a cutaneous nerve, supplying the outer side of the thumb and the skin of two and a half fingers. The posterior interosseous supplies all the muscles on the back of the forearm except the anconeus.

The branches of the musculospiral nerve, arising on the inner side of the humerus, consist of the muscular branches supplying the long and inner heads of the triceps, and the internal cutaneous branch which passes backward beneath the intercosto-humeral nerve and supplies filaments to the skin over the long head of the triceps. The posterior branches of the musculospiral nerve consist of a fasciculus of muscular branches which supply the outer and inner heads of the triceps muscle and the anconeus. The external branches consist of the external cutaneous branches and the muscular branches. The external cutaneous branches distribute filaments to the lower half of the arm on its outer and anterior aspect and the branch descending to the wrist distributes offsets to the lower half of the arm and forearm, on their posterior aspect. The muscular branches supply the supinator longus, the extensor carpi radialis longior and frequently a small branch to the outer part of the brachialis anticus (Quain⁶³).

Symptoms. The symptoms of injury to the musculospiral nerve vary in degree and duration according to the severity of the trauma and the resultant pathology. If, in a fracture of the humerus, the pressure on, or the stretching of the nerve is slight, any symptoms traceable to nerve injury may disappear in a few minutes. If continuity is interfered with, certain motor and sensory changes make their appearance.

Motor Changes. The wrist drops and the power of extension of the hand is lost. The hand is held pronated and half-flexed with the palmar surface slightly concave. If the hand is placed on a resistant surface, the lateral movements are impossible. If this deformity has existed for some time, there is a marked prominence on the dorsum of the hand, due to the stretching of the dorsal ligament of the wrist and the subluxation of the carpus. Extension of the fingers at the metacarpophalangeal joints as well as extension of the terminal phalanx of the thumb is lost.

The forearm is half-flexed and no extension is possible at the elbow.

Supination is entirely lost when the forearm is extended on the arm, but if the forearm is flexed, a moderate degree of supination is possible through the action of the biceps.

Sensory Changes. There may or may not be any loss of sensibility. The area of loss when the nerve is divided extends roughly over the dorsum of the hand and lower wrist. There is no loss of sensibility in the forearm beyond a slight impairment of a very small area to the faradic current, and even this is doubtful.

Several theories have been expounded to explain the slight changes in sensibility. Létiévant⁴⁵ attributes it either to the abundant anastomoses between the median and ulnar nerves which undertake regeneration when the radial nerve is injured, or to the newly-formed nerve fibers from the uninjured parts which grow into the anesthetic region and produce regeneration. Fessler²⁴ does not support this theory, but believes the fibers of the radial are important in the retention of the sensibility.

Pain. In complete division of the nerve no pain is experienced. If the nerve is injured or compressed by organized callus or scar tissue, the sensation of pain is most evident a few days after the injury.

Clinical Examination. In determining the extent of the injury it is necessary to obtain a careful history of the accident and symptoms, as well as to examine the injured parts and test all muscle groups and sensory areas.

If possible, it should be decided whether the nerve is completely divided or merely traumatized. The function may be lost below the seat of the injury, either because the nerve has been divided, traumatized, or compressed by callus. It is frequently difficult to judge the exact condition, particularly if the injured part is examined immediately after the accident, when the symptoms are severe. In such cases, the sensory examination is very frequently ineffective as numerous anastomoses exist in the hand, and the maximum puncture may be of no value. An electrical excitability test does not give deciding data, as it is rendered difficult through swelling, and excitability of the peripheral nerves may still be possible. The presence of motor signs may be of no value, as they may show remaining power or may indicate the beginning of repair.

Muscles. All the muscles supplied by the musculospiral nerve should be tested for movement, tone, reflexes and atrophy. The power of the extensors of the wrist should be tested with the fingers flexed on the palm, as any slight contraction in the extensors of the wrist may then be felt. The extension of the proximal phalanges should be noted. The extension of the thumb must be carefully distinguished from the movement of abduction, the latter being controlled by the median nerve. If the examiner discerns a slight trace of movement, spontaneous recovery may be expected.

Electrical Diagnosis. In making the electrical examination, the use of the Victor Multi-plex Sinusoidal apparatus with a diagnostic electrode and 6 by 8-inch discharging indifferent electrode is recommended in the U. S. A. Manual of Neuro-Surgery. The indifferent electrode is moistened and placed over the abdomen or back. The diagnostic electrode is applied over the motor point of each muscle to be tested. Sufficient current is used to obtain a contraction but not enough to stimulate the adjoining muscles. The patient lies relaxed. The faradic current is first used if a normal reaction to electrical stimuli is obtained. The presence of faradic irritability after ten to fourteen days means that the nerve will recover spontaneously, since it shows at once that reaction of degeneration is not present. If faradic irritability is diminished, then galvanic current is used and the speed of muscle contraction and the amount of current required, are noted. A feeble, sluggish contraction is an indication that the nerve has degenerated. A brisk galvanic reaction, even though faradic excitability is absent, is an indication to adopt an expectant line of treatment.

Skin. Methods for the examination of the sensory conditions have been outlined in the U. S. A. Manual of Neuro-Surgery. The epicritic sense is tested by shaving the skin and turning a camel's-hair brush over it. The protopathic sense is tested with a sharp pin on the end of a 6-inch stick. Deep sensibility is determined by the pressure of a pencil. It is rarely that some definite area of sensibility is not found following lesions of the musculospiral nerve.

Hamilton³² studied 55 cases at the Walter Reed Hospital to determine the areas of sensibility to pressure, pin-prick, and cotton or camel's-hair touch. He found that the patient fails to recognize subjectively and with any degree of accuracy the area of sensory loss, especially of the epicritic sense. Twenty-seven cases showed a definite area of sensory involvement in the forearm and hand. There was only 1 case in which the musculospiral nerve had been injured sufficiently high to produce loss of sensation corresponding to all three branches.

Vasomotor and trophic changes in the condition of the skin, nails, muscles, joints and bones should also be noted.

Types of Injuries. Injuries to the musculospiral nerve may be divided into two groups.

1. Immediate loss of function from traumatism.
2. Loss of function from pressure, callus, or scar tissue, usually associated with fractures, and occasionally following crushing injuries.

In primary division the onset of the paralysis is sudden. In secondary cases the paralysis develops insidiously and the functional loss increases as compression takes place. In case of injury coincident with or immediately following a fracture, the nerve may be bruised, stretched, compressed between the bone fragments or

impaled by a spicule of bone. The nerve may be completely divided or the fibers may be crushed without damage of the nerve sheath. Goldstein²⁹ found 12 cases of complete division out of 20 cases of paralysis due to injury at the time of fracture, and he believes that complete division usually occurs at the time of primary injury.

Complete division of the nerve results from fractures or from direct injuries such as occur in stabbing accidents. Such cases should be sutured as soon as possible. This type is illustrated by the following case.

CASE I. In the course of a fight this patient, T. G., had been stabbed in the right arm. Two months later he began to notice that he could not close his hand or pick up things. When we first saw him, four months after the injury, he had right wrist-drop, no sensation in the posterior radial side of the hand, and no power in the supinator longus or extensor groups. Operative interference was advised.

Operation. After a careful preparation, a 5-inch incision was made on the outer side of the arm. Upon exposure of the nerve, the upper end revealed a bulb almost as large as the end of the little finger, and the lower end was entirely separated and involved in scar tissue. By means of a safety-razor blade, $\frac{3}{8}$ of an inch was removed from each end. The nerve sheath was sutured with interrupted linen, and the nerve surrounded by fat. The muscles were sutured together loosely. The skin was closed with silkworm gut and the arm strapped in 45° flexion. A hyperextension splint was applied to the forearm and hand. This position was maintained for three months.

Six months after operation, power began to return in the wrist. Baking, massage and gentle movements were advised. Fourteen months after the operation, Dr. Earle E. Hussey, of Fall River, examined the patient and sent the following report:

At the elbow-joint, all motions were free and unlimited. The muscular power to flex and extend the forearm was very good. The patient complained of an aching sensation in the upper third of the forearm, but there was neither tenderness nor loss of sensation.

At the wrist-joint, the patient could move the hand freely in all directions. He could dorsiflex the wrist and had good power in the flexor and extensor muscles.

The Fingers. He could make a good fist; his hand grip was about one-half power. The power of flexion and extension was good. The terminal joints of all four fingers were stiff; all the other joints were free.

Loss of function may occur from hemorrhage which has become organized into scar tissue, which in turn involves the nerve and constricts the trunk.

CASE II. B. M., hurt her arm in an automobile accident in November, 1921. She suffered a deep muscle injury about 4 inches above and anterior to the external condyle. The wound healed in three weeks, but the patient was unable to dorsiflex the wrist and fingers. She was seen from the first time on December 27, 1921. There was a deep adherent scar, and considerable numbness over the lower external humeral region. The biceps and triceps were present and the patient could make a fist. There was no power in extension of the wrist or fingers, in spite of their having been held in hyperextension for six weeks. The patient had suffered also a fracture of the left clavicle and numerous other injuries. She was advised to enter the hospital for an exploratory operation.



FIG. 1.—Case II. B. M. Showing return of voluntary power in extension of wrist and fingers, one year and three months after freeing nerve from scar tissue.

Operation. January, 1922: After a careful preparation, the musculospiral nerve was exposed by a curved incision. The nerve was found to pass through scar tissue that had developed at the site of the wound. This scar tissue was excised and the nerve thoroughly freed. It was found intact and there was no bulbous end. The nerve was placed in a new muscle bed. The arm was kept at a right angle without motion for eight to ten weeks. The temperature remained normal. The wound was dressed for the first time on the fifth day. Seven weeks after the operation the patient was measured for a hyperextension splint for the fingers.

April 18, 1922. There was slight power in the extensors of the wrist.

May 16, 1922. The patient had regained power in the extensors on the radial side, but not on the ulnar. There were 20° of motion in flexion and limited extension in the elbow-joint, and it was

expected that these motions would increase. The patient was advised to continue massage.

August 4, 1922. The arm was greatly improved. The extensor return, except the extensor pollicis, was very good. Patient was advised to continue wearing the splint and to exercise the fingers daily for fifteen minutes.

September 6, 1922. The restoration of muscle control in the wrist was complete except for the extensor of the first metacarpal. The brace was discarded.

March 20, 1923. One year and two months after the operation, there was perfect flexion and extension at the elbow, good supination and pronation, and complete return of the musculospiral nerve distribution. The patient could separate the fingers. The thumb and index finger were slightly numb and the hand showed a little atrophy of the thenar eminence. The patient could not make a strong grip. (Fig. 1.)

Loss of function from pressure occurs following fractures of the humerus in which the nerve root is usually enveloped by callus or scar tissue that forms about the site of the fracture or injury.

CASE III. This was a case (J. L.) of injury to the musculospiral nerve following a comminuted fracture at the middle and the lower end of the left humerus with non-union. The nerve was compressed and caught in callus and scar tissue.

October 4, 1921. One year and six months after the injury, the patient was seen for the first time, and advised to have an immediate operation.

Operation. A lateral incision was made, exposing the field of non-union. The upper end of the musculospiral nerve where it enters the groove was located and dissected free from the groove for a short distance. As it then entered dense scar tissue it was necessary to locate the lower end of the nerve which was dissected upward from below. This lower end also entered the scar tissue, and it was only by careful and tedious dissection that the nerve was freely removed from this area without damage. (Fig. 2.)

The nerve was carefully examined and although there were a few areas of local swelling, no definite division had taken place, and there were no bulbous masses within the sheath.

The area of non-union was then explored and a graft removed from the tibia, was inserted and held in the humerus by kangaroo suture. A new bed was made for the musculospiral nerve and the wound closed.

A plaster was applied from the fingers over the shoulder and about the chest. The wrist was held in hyperextension.

January 24, 1922. As the radiogram showed no union, the cast was not removed.

March 27, 1922. Callus formation was beginning and the graft

was firm. The plaster was taken off (now six months), but protection was continued.

January 22, 1924. Union was solid. The shoulder was normal. Flexion and extension were perfect. Supination was limited a few degrees. The patient could make a fist, but the fourth and fifth fingers were contracted at the second phalangeal joints. There was complete regeneration of the extensor control. The patient was back at work and had a very functional hand.

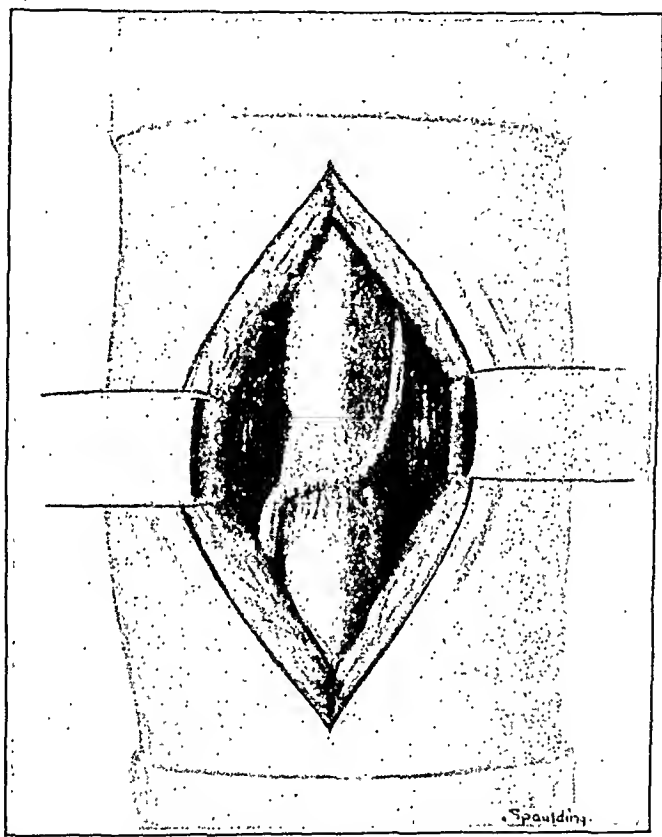


FIG. 2.—Case III. J. L. Showing area of non-union with musculospiral nerve caught in cicatricial tissue.

Prognosis. In general, operative results have been satisfactory. Kramer⁴³ reported 35 cases with only 3 poor results. Blenke⁵ reported 58 cases, 41 of which made complete recovery, 6 partial recovery, 8 improved, and 3 showed little improvement. In some cases failures have been due to neglect of aseptic requirements or to lack of postoperative care.

Surgeons disagree as to whether recovery is better after nerve suturing for primary injuries, or following operation for paralysis due to the involvement of the nerve in scar tissue or callus formation. Sherren⁷³ and others have found that recovery may be perfect after a primary suture, but that it is not so good following secondary

operations, as sensory recovery is rarely perfect. Borchard,⁶ on the other hand, claims that operation for secondary injuries results more favorably because in primary suture any neglect of aseptic requirements is followed by failure of nerve suture.

Although the prognosis is better if the interval between the injury and operation is short, still there is a chance of complete recovery after a long period of paralysis. Cases operated after sixteen months or even after three and a half years following fracture have resulted in complete restoration of function.

The establishment of continuity by end-to-end suture offers a greater chance of success than any other operative procedures such as grafting, implantation, or transplantation of nerve.

Indications for Exploration. Any open wound over the musculo-spiral nerve accompanied by wrist-drop, should be enlarged and the nerve examined. If a division of the nerve is present, a suture should be done at once.

If the nerve is injured from a blow in which it seems probable that complete division has taken place, suturing should be done early. Sometimes, however, the bruised condition of the soft parts is such that it is necessary to postpone a needed operation until the hemorrhage is reabsorbed, and a favorable opportunity offered for the healing of the wound. If the exact condition of the nerve cannot be determined, it is well to wait to see if power returns spontaneously. During this period, however, the fingers and wrist should be held in hyperextension, which position always favors the return of muscle power.

In the presence of fractures accompanied by radial paralysis in which it is impossible to determine whether paralysis is due to contusion or sectioning, it is best to first obtain reduction of the fracture and apply plaster. The muscles should then be watched for signs of atrophy and the fingers and the thumb should be exercised daily. If, after three or four months, paralysis still persists, exploratory operation should be performed.

Operative Technic. The method of treating the nerve must vary according to the pathological findings. If the nerve is found intact, often only a simple operation, such as removing the bone over which the nerve is stretched, or removing scar tissue or excessive callus, may be necessary to give relief.

Frequently, however, the nerve may be completely divided, constricted, torn, or bulbous at one end. In such cases, the usual procedure is to excise the affected portion, freshen the nerve ends, and establish continuity by suture. Nerve sutures have given very gratifying results and are recommended by many operators, including McCurdy,⁴⁸ Keen,⁴² Cheyne,¹³ Eve,²² Ashhurst,¹ Auvray,² and many others.

AUTHOR'S TECHNIC. The approach to the part of the nerve involved is most successful if the upper and lower parts outside

the field of injury are located and a dissection made up and down to the seat of damage. This approach is not only much safer but quicker than other method. When the ends of the nerve are found bulbous, or a distinct swelling or constriction is felt in the nerve trunk, it is best to cut out this section by means of a safety-razor blade. The ends are then approximated and the entire sheath about the nerve sutured with linen. In cases of division of the nerve in which retraction has taken place it is often necessary to place the arm in flexion to gain approximation. It is rarely necessary to shorten the humerus.

After the ends have been sutured, the nerve should be placed in a new non-scar tissue bed, usually between layers of fat or muscle. There is some discussion as to whether fat is the best substance to prevent the formation of adhesions. Henle,³⁵ Morris⁵⁰ Williams,⁸¹ and many others approve its use. Other operators believe that the fat atrophies, and they recommend the method used by Fessler²⁴ and Grisson,³¹ of wrapping the nerve in a muscle flap of the triceps or of the brachialis.

The elbow should be held in flexion for at least five to six weeks, and then gentle passive motions may be started. The wrist and fingers must be held in hyperextension to avoid flexion contraction, to favor muscle regeneration, and to prevent the stretching of the extensors which, in itself is an important factor in hindering the return of muscle power.

As soon as motion begins to return, graduated massage and muscle training are of great advantage. The time when improvement begins varies from a week to several months. Motion usually begins to return in three or four months and it is usually a year before restoration is complete.

It may happen that after excision of the affected portion of the nerve, too large a gap exists to allow the approximation of the nerve ends. Such a condition is not frequently found in civil life, but war injuries often destroy a large part of the nerve. Several means have been used to bridge the space.

Piper,⁶⁰ Morton,⁵¹ and Sherren⁷³ advised the manual stretching of the nerve and suture after the ends were in apposition.

Plastic neurotomy was used with success by Harrison³³ who turned into the space a flap from the upper end of the nerve which was bulbous. Dawbarn and Byrne¹⁵ bridged a 3-inch gap by splitting the nerve at a low point of its distal portion and swinging the long shaft thus made into the space. Sherren⁷³ believed a flap should be used as rarely as possible, because such an operation necessarily is technically complicated.

Implantation of nerve, the method of attaching the stump of the distal end of the severed nerve to a healthy nerve, was first proposed by Lobker.⁴⁶ Roques de Fursac⁷⁰ implanted the musculospiral nerve in the median. Barkley³ anastomosed the proximal

and distal ends with the median. Auvray² formed an anastomosis of the lower end of the radial with the internal brachialis cutaneous nerve. These procedures are of little value if the fibers of the healthy nerve are not separated and such an operation is difficult.

A few successful results from nerve grafting have been reported. Auvray² transplanted successfully a portion of the internal brachialis nerve 10 to 12 cm. long between the two freshened extremities of the musculospiral nerve. Sherren⁷³ suggested using for grafts the internal saphenous nerve obtained from the patient or from a recently amputated limb. Neuhoof,⁵⁷ in a recent article on the transplantation of nerves in general, stated that as yet it was impossible to estimate the value of nerve transplantation. Only a few successful results have been obtained and the cases in literature have been recorded too early to judge the final result.

Still other means of bridging the gap have been suggested. A tubular suture has been proposed by some surgeons. Sherren⁷³ preferred a tube composed of one of the patient's superficial veins. Foreign materials have also been used. Keen⁴² applied catgut threads, and Morris⁵⁰ bridged a gap of 3 cm. with silk thread. Magnesium was tried, but it was found to harden. Reisinger⁶⁸ proposed sinking the nerve in the triceps muscle and fixing it there.

Resection of the humerus as a means of allowing the approximation of the nerve ends is justifiable only in cases of ununited fractures complicated by division of the nerve. Ollier⁵⁹ has reported early cases of resection. Keen⁴² reported using this method in 1 case and Riethus⁶⁹ in 3 cases.

If the damage to the musculospiral nerve is irreparable by the use of any of the methods mentioned, or if a case has not been relieved by end-to-end suture, then tendon transplantation is a commendable procedure. Its object is the improvement and restoration of muscle balance in the hand.

As the extensors of the wrist and fingers have lost their power, the problem is to transpose some of the muscles on the flexor aspect of the forearm without interfering with the power of flexion. The flexor carpi radialis, the flexor carpi ulnaris, and the pronator radii may be relied upon for this procedure.

AUTHOR'S TECHNIC. The attachment of the flexor carpi radialis is severed through a 1-inch incision made directly over it on the anterior surface of the wrist. A second incision is made half way up the forearm along the course of the flexor carpi radialis tendon, and the tendon pulled up. A long L-shaped incision is made across the back of the wrist and up the side of the ulna. The flap is dissected upward, the tendon of the flexor carpi radialis is thrust obliquely over the edge of the radius and made to appear over the back of the lower end of the radius. (Fig. 3). The ulnar tendon is severed at its attachment, carefully dissected upward as far as the

incision permits, and the whole muscle turned over, so that the tendon lies along the back of the lower end of the ulna.

During the completion of the operation the wrist and fingers are held in hyperextension. All the extensors are split to receive

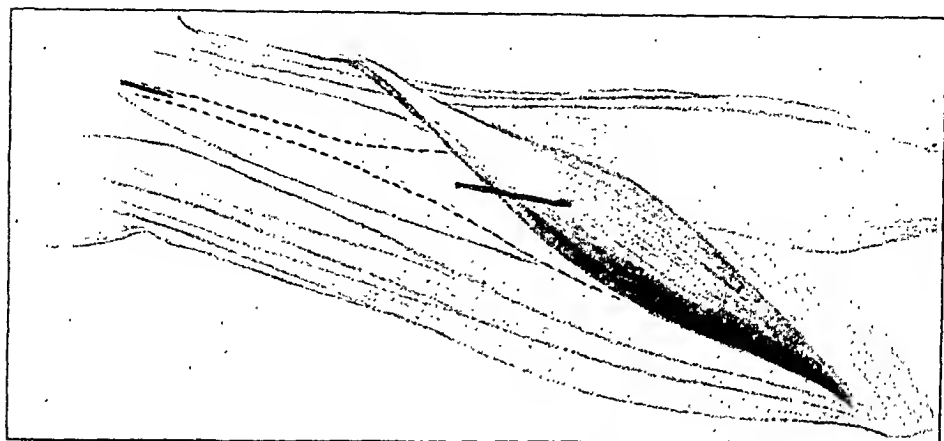


FIG. 3.—Showing incisions over attachment of flexor radialis and along the course of the tendon. The tendon is thrust obliquely over the edge of the radius.

these tendons, which are crossed through them (Fig. 4.). The thumb extensors are also included in those cases in which special provision has not been made for the extension of the thumb by the use of the pronator radii teres or the palmaris longus.

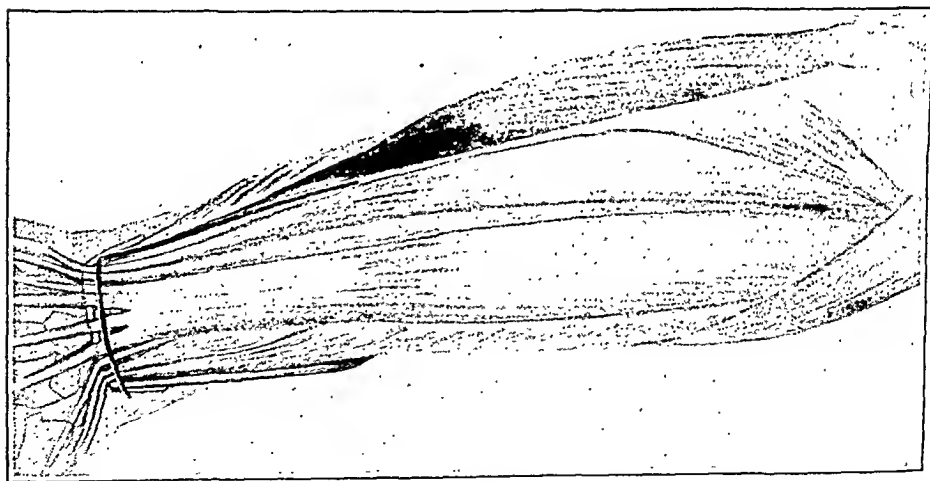


FIG. 4.—Showing the L-shaped incision across the back of wrist and up the side of ulna. The ulnar tendon has been severed at its attachment and the whole muscle turned over. The radial and ulnar tendons are seen running through the extensors which are slit to receive them.

The wound is closed. A splint is applied with the wrist and fingers held in hyperextension. This is worn for six to eight weeks during which time massage and passive motion are carried out.

CASE IV. F. A., was ill in 1916 with acute arthritis of the shoulder. After an operation in which some dead bone was removed, wrist-drop and loss of elbow motion were noticed.

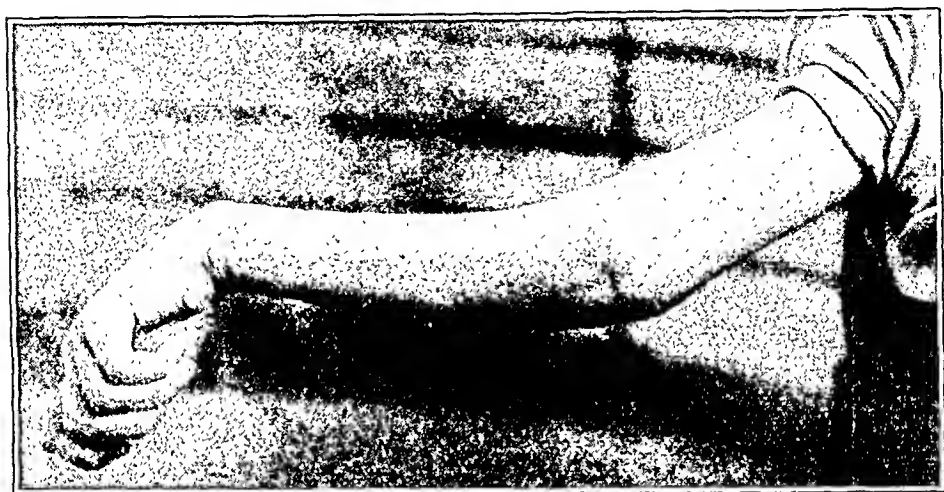


FIG. 5.—Case IV. F. A. Showing wrist-drop and hand deformity before tendon transplantation.

January, 1917. The patient was seen for the first time. Radiograms showed a diffuse osteomyelitic process involving the whole humerus. The shaft was opened *in toto* and four days later the patient was able to extend the fingers, showing some power in the radial nerve.



FIG. 6.—Case IV. F. A. Hand in splint after tendon transplantation.

September, 1917. The patient discarded the leather brace he had been wearing and a small hyperextension hand splint was applied. A radiogram later showed complete regeneration of the humerus. Daily olive oil massage and constant use of the hand were advised.

November 5, 1919. The power of extension of the wrist had not been regained (Fig. 5). A tendon transplantation was performed according to the above technic.

November 29, 1919. Massage and muscle training were started.

December 8, 1919. The patient was able to hyperextend the wrist.

September 8, 1920. He had voluntary extension of the wrist to within 15° of normal, and voluntary extension of the fingers to within 20° to 40° of normal. The extension of the thumb was deficient, but satisfactory (Fig. 6).

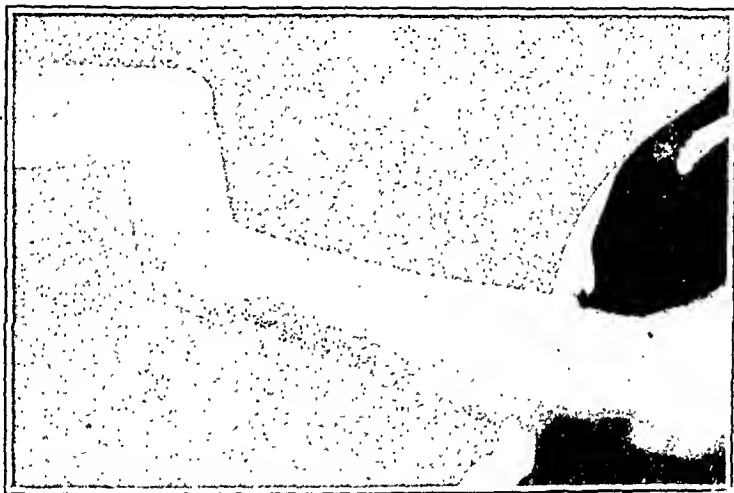


FIG. 7.—Case IV. F. A. Voluntary extension four years after tendon transplantation.

CASE V. M., admitted to the Alder Hey Hospital September 26, 1917, had suffered a compound fracture of the right humerus and severance of the musculospiral on May 9, 1915.

History. He had been treated in France, having had 7 operations for removal of shrapnel and cleaning of wound. The last operation was supposed to have been on the nerve.

Examination. The wound had been healed eight months. The present complaint was wrist-drop. Two long scars were attached to the bone in the upper arm. The humerus was shortened and irregularly thickened in middle and lower thirds. There was no power in the extensors of forearm. There was slight sensory loss over first phalanx of thumb. From the depth of the density of the scars, a wide gap of nerve seemed probable.

Electrical Reactions. The median and ulnar sensations were not affected. The radial sensation, E. and P. was impaired on the whole dorsal surface of the thumb, and slightly over the knuckle of the index finger. The forearm sensation was not affected over the musculospiral area. The extensors of the thumb, F.a., G.

faint, K. C. C.) A. C. C. Ext. communis, F.a., G. fair K. C. C.) A. C. C. The ulnar and median muscles were normal.

Diagnosis. The musculospiral nerve was involved in callus.

Treatment. On October 9, 1917 an operation was performed by Dr. A. R. MacAusland. Through a 5-inch incision, the musculospiral nerve was exposed just above the elbow, and followed up about an inch into very dense scar, where its course could not be traced farther. Without disturbing this region to any extent, the nerve was exposed on the axillary side as it entered the musculospiral groove, where it was found to be free for a short distance. It then entered dense scar tissue, but was carefully traced for about 1 inch more to the region of the very deep posterior scar. The dissection was completed through the incision on the outer side of the arm. The nerve ran into scar with only slight tendency to bulb. Exploration of scar farther revealed no nerve elements. The gap of about 3 inches was filled in with a section of the cutaneous nerve from the inner side of the musculospiral nerve in the axilla. It was not possible to bring the nerve ends together with graft, even by the expedient of crossing it in front of the humerus.

October 12, 1917. No pain, no temperature.

October 23, 1917. Clean; healed. Tendon transplantation seemed advisable.

November 13, 1917. Operation: Tendon transplantation. Flexor V. rad. into extensors of thumb, extensors longior and brevior and other extensors.

November 14, 1917. The patient had considerable pain. The circulation was good.

November 19, 1917. The patient was much more comfortable. He was advised to wear a long cock-up splint, with strap and thumb piece.

November 23, 1917. The thumb was to be extended. The wound showed slight sepsis.

November 26, 1917. The wound was clean. A short cock-up splint was to be applied.

Transplantation of the tendons for musculospiral nerve paralysis has been a most successful operation, as the tendons used are constant and strong. The early attempts to convert tendons into ligaments were made by Tilanus,⁷⁵ Codivilla,¹⁴ Reiner,⁶⁷ and Gallie.²⁶ Jones,³⁹ Francke,²⁵ Müller-Aachen,⁵⁴ Vulpius,⁸⁰ Drobnik,¹⁹ and Murphy⁵⁵ advocated this procedure in cases of extensive destruction of the nerve.

Jones³⁹ has outlined a tendon transplantation operation in which he converts the three extensors into ligaments so that the carpus can be fixed in the best functional attitude of dorsiflexion and still permit movement at the wrist-joint, but not in the direction of the deformity.

His operative technic consists of making a $3\frac{1}{2}$ -inch incision from just above the back of the wrist-joint extending up the middle of the forearm. By retracting the extensor ossis metacarpi pollicis and the extensor brevis pollicis, the two radial extensors may be followed along the forearm and divided high up and the ends pulled down. A tunnel is then drilled across the radius from the outer side, a little over an inch above the line of the wrist-joint. After the tendons have been scarified the extensor carpi radialis longior is pulled through the tunnel from the outer side and the breviar from the inner side. Their ends overlap and are sewed with a continuous catgut suture. In the same way the extensor carpi ulnaris is followed up to the forearm, divided, and the ends drawn through a tunnel in the ulna. Any tendency toward radial deviation of the hand by the pull of the radial extensor is thus corrected. The hand and forearm are encased in plaster. It is important to support the hand in the dorsiflexed position from the time the first catgut suture is inserted until the last plaster bandage is applied. In two or three months the patient may use his hand.

In a case of complete paralysis of the nerve Müller⁵⁴ tried tendon transplantation by cutting the tendon of the flexor carpi ulnaris and uniting it with the extensor tendons of the fingers. Seven months later the tendon of the flexor carpi radialis longus was cut and sutured to the tendon of the abductor of the thumb and the extensor carpi radialis longus. The patient was then capable of lifting the hand to a horizontal position and of abducting the thumb.

Murphy⁵⁵ released the flexor carpi radialis dorsally for 4 inches by tunneling through a button-hole incision. It was passed subcutaneously downward to the upper margin of the posterior annular ligament. The extensor tendons of the thumb and of each finger (two for the index and two for the little finger) were transfixed. The tendon of the thumb and of the index finger were attached obliquely from above downward and inward so that extension would not bring the inner three fingers into play ahead of the thumb and index finger.

Vulpis⁸⁰ reported 28 cases of tendon transplantation and Drobni¹⁹ reported 16 cases.

Sir Robert Jones⁴⁰ makes use of the pronator radii teres to produce extension of the wrist, by inserting it into the two radial extensors, and the flexor carpi radialis and the flexor carpi ulnaris to produce extension of the fingers and thumb by insertion into these tendons. During the whole procedure of tendon suture he keeps the wrist and fingers in complete dorsiflexion and the thumb in full abduction in order to procure the best action from the transplanted tendons. After operation the limb is placed in a splint which keeps the wrist in full dorsiflexion and the metacarpophalangeal and the interphalangeal joints flexed at an angle of about 10° .

Jones has used this technic in 20 cases. All the patients were

able to dorsiflex the wrist with the fingers closed and then to extend the fingers while the wrist remained in dorsiflexion.

Pathology. In operating for musculospiral nerve paralysis, the nerve is often found intact, but stretching over bony fragments or involvement in scar tissue or callus prevents it from having normal power.

If the nerve is crushed or torn the changes differ from those which occur as the result of severing by a sharp knife. In the latter case there is no contact between the two ends of the nerve and the changes differ in the proximal and distal parts. The proximal end becomes markedly bulbous. The distal end becomes shrunken, tapering, or slightly bulbous.

If the nerve is crushed it becomes inflamed and the inflammatory condition may lead to complete destruction. The nerve sheath may not be damaged, but the nerve fibers being inflamed, a constriction or a bulbous formation may develop within the sheath.

Reparative Processes. The regenerative process depends upon the trauma, the pathology and nourishment of the nerve.

Henriksen³⁶ made experimental investigations to determine the exact regenerative processes in a nerve that was completely divided and in one damaged in a crushing injury. He found that after complete division regeneration begins immediately, developing most rapidly in the central stump where fully organized myelin fibers may exist as early as ten days after injury. The first histological sign of regeneration is activity of the neurilemma nuclei which begin to proliferate. The protoplasm at the poles of the nuclei increases and grows into thin threads through the old Schwann sheaths and out into the severed nerve ends forming a bridge between the latter. Henriksen found that in the course of a few days these threads may bridge a gap of more than 0.5 cm., and that the old Schwann sheaths are pierced by long protoplasmic threads before the old threads have completely lost their structure. Fully characteristic nerve segments may be found in the central stump ten days after severance.

When a nerve is severed, its muscle loses weight and degenerative changes occur. At the same time the sarcolemma nuclei become active and new cellular matter forms in the muscle. When innervation begins, these cells form the basis for the formation of young muscular fibers. It is difficult to tell just when the muscle regains tone, but it may be late, five to six weeks after a primary suture.

Henriksen, in experimenting on rabbits, could find no essential difference in the process of regeneration when the nerve was sutured or when it healed unaided. In fact, the nerve fibers were at first found deflected as a result of the pull of the thread, although later they straightened out. Nerve suture, however, is necessary when obstacles prevent spontaneous healing.

One would naturally assume that a crushed nerve would regenerate

more easily and quickly than a severed nerve, but clinical examinations show that physiological restitution is often not so complete and is often slower in a case of a crushed nerve. The nourishment may be established more rapidly, but disturbances may appear in the process of regeneration, or the myelin differentiation may be disturbed, thus hindering the healing. After a complete severance of the nerve, the mass growing out from the ends to form the bridge between the ends thickens, and the nerve recovers its smooth appearance. If the nerve is crushed the thickness is uneven and it infiltrates the surrounding tissues. The peripheric part of the nerve is swollen and edematous.

Literature. After von Busch¹⁰ and Ollier⁵⁹ in 1865 reported good success in operating in cases of paralysis following fractures of the humerus, many similar cases were recorded in literature. In 1886, von Bruns⁹ reported 189 cases of nerve injuries. Seventy-three of the 138 cases of the upper extremities were musculospiral nerve paralysis following fractures of the humerus.

In 1889 Bowlby⁷ issued statistics of the operated cases that had been published. All the cases, 2 by Trélat,⁷⁷ 2 by Bidder, 1 each by Erickson, Ollier, Whitson, Delans, Israel,³⁸ Tillaux,⁷⁶ and Hueke had resulted from fractures of the humerus and were due to stretching, contusion or pressure. The results in 7 of these cases were satisfactory.

Goldstein²⁹ in 1892, Wölfler⁸³ in 1895, Neugebauer,⁵⁶ Zoegemanteuffel,⁸⁴ and Drewitz¹⁸ in 1895, reported several cases in which the nerve was found compressed in scar masses or bony callus. Successful results were obtained by operative interference.

In 1899 Riethus⁶⁹ described fully 7 of his cases. In 5 cases the nerve was compressed by bony callus or fibrous tissue. Complete cures were effected by operative interference in 2 of the cases and essential improvement was obtained in 2 cases. The result in the fifth case was not reported. Excellent results were obtained in 2 other cases in 1 of which the nerve was stabbed on the edge of a fragment of bone, and in the other in which the nerve was stretched over a sharp bony edge.

The same year Willmers⁸² reported a successful result.

In 1900, Keen⁴² reported a series of 7 cases, in 6 of which operations were performed for paralysis of the musculospiral nerve following fracture of the humerus. Complete restoration of function was secured in 2 cases by suture of the nerve. A useful arm was obtained in 1 case in which the humerus was resected to approximate the ends of the nerve over a gap of 5 cm. As the other patients did not carry out the postoperative requirements, very little improvement took place in 2 cases and no improvement in 1 case.

In 1 case of complete division of the nerve by a knife blade, Keen sutured the nerve ends with silk thread. Fourteen months later the patient had a good, useful hand.

Launois and Lejars⁴⁴ reported a successful case in paralysis following a fracture.

Braüninger,⁸ Kramer,⁴³ and Reisinger⁶⁸ also reported good results in freeing the nerve from compression.

In 1905, Piper⁶⁰ published his monograph on the subject of musculospiral nerve paralysis following fractures of the humerus. After reviewing the literature from early times and describing the various types of operative technic, he cited 4 cases from the Kieler Clinic. One case was not operated. The second in which the nerve was pleated and a layer of the triceps laid between it and the bone, resulted in a weak hand. In the third case the nerve was found intact, but twisted above the seat of fracture; paralysis was overcome by freeing the nerve. In the fourth case the nerve was intact but involved in callus. The definite outcome of the operation was not recorded, but the latest record was the beginning of a degenerative reaction.

Cudder and Paul⁷¹ reported 11 cases of suture in the Massachusetts General Hospital. Eight cases were relieved by operation. The other 3 cases were failures.

Of 12 cases reported by Borchard⁶ in 1907, 2 were unsuited for operative handling; in 2 cases the nerve was sutured; in 3 cases it was simply loosened from adhesions; in 3 cases bony masses and scar tissue were removed; in 1 case it was necessary to excise the radial head, and in the twelfth case nerve grafting was employed to bridge a large defect. Except in the last 2 cases on which it was too early to report, the condition was cured by operation.

In 1909, Harrison³³ reported 2 cases, 1 in which the nerve was compressed by callus and 1 in which the nerve crossed in front of the humerus. Operation on the first case in which a flap of the nerve was turned in to bridge a wide gap, resulted in a good serviceable hand. In the second case it was necessary to divide the humerus in order to place the nerve in position. In three and a half months the patient could extend his hand to an angle of 150° with the forearm, and further improvement was expected.

Els²¹ reported 2 cases of secondary suture. Perfect function resulted in the first case from operation for partial tearing of the nerve over a bony fragment. The result in the second case of paralysis due to the involvement of the nerve in scar tissue, was good, but the hand was somewhat weak.

Charbonnel¹² reported a case of double fracture and splintering of the humerus followed by nerve paralysis. The nerve was freed from between the long supinator and the anterior brachialis, and in six and a half months the patient had normal movements.

Barkley³ reported a case in which the humerus was broken in two places, and there was a loss of 4 inches of substance of the nerve. The ends were anastomosed with the median nerve, and complete use of the hand resulted.

In 1911, Morestin⁴⁹ reported 3 cases on which he had operated. In 1 following fracture of the humerus, the nerve was freed from between the fragments and sutured, and in one month there were good prospects for success. In the second and third cases of paralysis, likewise following fractures, the nerves were found embedded in callus. Fifteen days after operation in the second case, the patient could extend the hand and fingers almost to normal. Operation on the third case also resulted in the return of all normal movements.

Schwartz⁷² operated for a case of paralysis following fracture of the humerus. He freed the nerve from callus and interposed a layer of muscular and fibrous tissue between it and the bone. In ten months recovery was complete.

Gaudier and Deladrière²⁸ reported a case of paralysis following fracture of the humerus. Five months after the nerve was freed from adhesions the patient had recovered all movements.

In 1912, Nikoloff⁵⁸ cited a case in which the paralysis appeared three weeks after the healing of a fracture of the humerus. To bridge the gap, a tube of fibrous cord was made and the non-paralyzed end of the nerve sutured to the paralyzed end. A muscle layer was inserted to separate the nerve from the bone. A complete return of movement was obtained.

Judet⁴¹ cited a case of secondary paralysis following fracture of the humerus in which the nerve was found compressed by a spicule of bone. Operation resulted in a complete cure.

Ferraton²³ sutured a nerve that had been destroyed in a comminuted fracture of the humerus caused by a bullet. All movements of the hand returned.

Murphy⁵⁵ reported establishing end-to-end union of the nerve by applying a flap. In another case he united the ends of the nerve at the central septum to the triceps muscle. He did not report his results.

Gallois and Tartanson²⁷ reported 2 successful cases in which paralysis had followed fractures. After isolation of the nerve from the callus, a layer of muscle was inserted between it and the bone to prevent further complications.

In 1914, Mosti⁵² cited a case of secondary suture that resulted in complete success. Quénu⁶⁴ also reported a successful case of secondary suture. Hohmann³⁷ operated on 1 case of paralysis following fracture of the humerus.

In 1916, Dawbarn and Byrne¹⁶ did a splitting neuroplastic operation in a case of destruction of the nerve from a fracture of the humerus. An irregular form of regeneration resulted.

Successful results from suturing of the nerves were reported by Souques,⁷⁴ Loewenstein⁴⁷ and Ranschborg.⁶⁵ Moszkowski⁵³ presented a case in which a pedicled flap of the triceps muscle was used to bridge the defect in the nerve. At the time of his report

it was too early for complete restoration but signs of regeneration were apparent. Two successful nerve suture operations for complete division of the nerve were presented by McCurdy⁴⁸ in 1917.

Beck⁴ operated for a paralysis resulting from a fracture that had occurred seven months before. In operation a tubule of fascia lata and fat was transplanted into the extensor tendons. Twelve weeks after the operation, considerable power had returned to the muscles.

Morris⁵⁰ reported a successful case of secondary suture for paralysis following non-union of a fracture of the humerus. In discussion of his report, Green and Hitzrob reported similar cases in which they had been successful.

Hartwell³⁴ reported a case of a successful suture forty-six days after section of the nerve by a stab wound.

Due to the frequency of injury to the musculospiral nerve in war wounds, there were many operations performed between the years 1917 and 1921. Gosset,³⁰ in 1923, summed up very well the results of these operations.

In 1917, Gosset,³⁰ himself, reported 144 cases. In 44 cases of freeing of the nerve, there were 26 successful results, 10 cases of improvement, and 8 failures. In 27 cases of suture for complete sectioning, there were 16 good results, 1 case of improvement, and 10 failures. In 2 cases of suture for incomplete sectioning, there was 1 cure and 1 failure.

In 1918, Gosset and his pupil Charrier studied 76 cases. In 18 cases in which the nerve was freed from compression, 95 per cent recoveries were obtained. The condition of the other patients was improved. Thirteen cases of complete sectioning in which the nerve was sutured, resulted in 4 recoveries and 3 failures due to bad technic. The condition of the other 6 patients was slightly improved. In 21 cases of incomplete sectioning, there was a fibrous formation between the nerve ends which some operators believed might be used as a means of conductivity. In the 5 cases in which this tissue was utilized there were 4 failures. In the other cases the fibrous formations were excised and an end-to-end suture was done. There were 9 good results, 4 cases of improvement, and 3 failures. These results show clearly that the fibrous formations do not act as conductors of nerve influence.

Dumas²⁰ reported the results of 115 cases that were operated upon. In 18 cases of freeing the nerves from compression, 83 per cent good results, and 11 per cent fair results were obtained; in 41 cases of incomplete severance 70 per cent successful results and 11 per cent fair results; in 46 cases of sectioning with some fibrous continuity remaining, 43 per cent successful results, 10 per cent fair results and 46 per cent failures; in 10 cases of complete severance treated by suturing, 1 fair result. The other cases were failures.

In 1918, Delagénière and Tinel¹⁷ reported 181 sutures with 88 per cent positive results. Villard⁷⁹ reported 8 suture operations with 4 good results.

Reder⁶⁶ reported a case of complete paralysis caused by a shot wound. At operation a strip of muscle taken from the head of the triceps was wound around the point of injury. In forty weeks all movements, except the ability to pick up a pin, were possible.

Auvray² in 1919, collected the results of 31 cases of wounds of the nerve operated in 1915. Of 15 cases of simple freeing of the nerve from compression, 7 patients obtained complete restoration of function; 4 an improved condition, and there was 1 failure; of 11 cases of end-to-end suture, 8 patients obtained complete restoration and there were 3 failures; 1 case of excision of a cicatricial nodule from the middle of the nerve was successful; and 1 case of nerve graft 10 to 12 cm. long from the internal brachialis cutaneous nerve resulted successfully. Three cases of anastomosis and redoubling of the upper end of the nerve were failures. On the average Auvray found amelioration had begun at the end of several months, usually four to eight.

In discussion of Auvray's report Wiart cited statistics less satisfying. Of 25 sutures, there were only 5 complete cures, and 5 cases of improvement; of 61 cases of freeing the nerve there were 20 complete cures, and 20 ameliorations.

In 11 cases of suture, Cestan¹¹ obtained 5 complete cures. The condition of 4 other patients was improved by operation. Two cases were failures.

Putzu⁶² obtained 85 per cent cures in operations of freeing the nerve and 47 per cent cures in suture operations. Dane¹⁵ secured 50 per cent good results. Platt⁶¹ collected 35 cases of nerve suturing in which 26 very good results were obtained.

From the results of the above cases it is seen that operations of freeing the nerve give 95 per cent good results and suture operations give 45 to 55 per cent.

Henriksen,³⁶ in 1923, reported 5 successful cases in 2 of which the nerve was sutured, in 1 4 cm. of the humerus was resected to bridge a gap of 6 cm., and in 2 cases the nerve was freed from callus.

Conclusions. 1. The nerve may be injured in three ways: The nerve trunk may be crushed without damage to the sheath; the nerve may be completely divided; power may be lost through the involvement of the nerve in scar tissue or callus.

2. Early recognition and treatment of nerve injuries in connection with fractures and severe traumatism is very important. We may expect a perfect result in cases of immediate suture of the nerve. While intervention in cases of old standing has given good results, it is the general opinion that the chances of success are lessened after the elapse of a long period of paralysis.

3. Simple freeing of the nerve is very often the only procedure necessary to relieve the condition. In cases of complete division of the nerve or in cases in which there is need to excise a portion of it because of a fibrous formation, nerve suture has been found the most satisfactory procedure for the approximation of the nerve ends. If the nerve suture does not relieve the condition, or if the case is not reparable by the various methods of manual stretching, neurotomy or nerve grafting, then tendon transplantation gives satisfactory results.

4. After severance of a nerve, healing begins spontaneously. In cases of nerve suture function develops in the same manner as in spontaneous healing. After secondary suture sensibility returns early. Muscle control usually appears in the course of two to four months and is complete in from six to nine months, depending upon the location of the nerve injury.

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A RAPID METHOD FOR THE DETERMINATION OF GASTRIC ACIDITY BY MEANS OF TEST PAPERS.

BY W. DENIS, PH.D.,

AND

D. N. SILVERMAN, M.D.,

NEW ORLEANS.

(From the Laboratory of Physiological Chemistry and the Department of Medicine of the School of Medicine, Tulane University, New Orleans, La.)

THE determination of "free" gastric acidity by titration with 0.1 N sodium hydroxid and dimethylaminoazobenzol (Töpfer's reagent) is a method which has found practically universal acceptance in the clinical laboratories in this country, and which has retained its popularity in spite of adverse criticism from several sources.¹

In view of the fact that gastric digestion is dependent on the hydrogen-ion concentration of the stomach contents the idea of substituting a colorimetric hydrogen-ion determination for the titration method has been suggested by several investigators,¹ but most of these procedures have been rather too cumbersome to become popular in clinical work, on account of the large number of indicators and standard buffer solution required; the simplest and most practical being that suggested by Shohl and King in which one indicator, thymolsulphonephthalein, is employed together with a set of standards sealed in glass tubes, which if left in a dark place retain their original color for a relatively long time.* The method of Shohl and King, simple as it is, is sometimes difficult to carry out in the crowded clinic on account of the fact that as a preliminary it is necessary to centrifuge or filter the contents, and also because we believe that in order to get reliable results it is essential that a liberal supply of distilled water be on hand with which to rinse the glassware to be used in this test.

For more than a year we have been making use of test papers for the approximate determination of the pH of gastric contents. The use of test papers for this purpose is not new. McClendon,² in 1915, described a series of nine different test papers to be used in gastric contents and four for duodenal contents, and states that in his opinion the test paper is but little less sensitive for the determination of hydrogen-ion concentration than are solutions of the same dyes. Further experiments on the use of test papers for pH determinations in biological fluids have been described by Hass³ and also by Felton.⁴

We have endeavored to prepare a single test paper which could be used with gastric contents of all degrees of acidity, but so far our search has been unsuccessful, and we have been compelled to

* A set of these standards which has been in more or less constant use for two years has recently been checked and found to be unchanged.

make use of papers prepared from two different dyes. Thymol blue for the range from pH 3.0 to pH 2.0 and dimethylaminoazobenzol (Töpfer's reagent) for the range from pH 2.0 to pH 1.0.

The papers are as follows: A solution of the dye in 95 per cent alcohol (0.5 per cent for dimethylaminoazobenzol, and 0.1 per cent for thymol blue) is poured over a sheet of filter paper six inches in diameter, the excess dye allowed to drain off, and the paper dried quickly by holding it in front of a rapidly revolving electric fan. The papers are then cut in strips of approximately 1 by $\frac{1}{4}$ inch in size, and stored in some receptacle in which they are protected from light and from the fumes of the laboratory. Only the highest grade of smooth "quantitative" filter paper should be used. We have obtained good results with the Arthur D. Little quantitative filter paper and with Whatman's No. 44, but probably any other grade of ash free paper would do as well. The gastric contents is removed in the usual way after an ordinary test meal, and a small portion of the material collected is poured over one end of a test paper. From the table of colors tabulated below it is then possible to tell at a glance whether we are dealing with hyper, normal, hypo, or anacidity. If a series of buffers of known pH are available a small quantity of one of these solutions of a reaction similar or nearly similar to what is believed to be the pH of the gastric contents (as determined by the color produced by it on the test paper) may be poured on another piece of the paper and the color so obtained compared with that produced by the unknown, but such a procedure while it is useful as a check on the readings, is not absolutely essential to one familiar with the colors produced. All readings should be made as soon as the solutions are poured over the papers, as the colors tend to change on standing.

An excellent series of buffers for this purpose may be prepared by following the directions published by Shohl and King,¹ or they may now be purchased ready for use in 100 cc portions from the La Motte Chemical Company of Baltimore. The buffers which will be found most useful are the following: 1.4, 1.6, 1.8, 2.0, 2.4, 3.0, which will cover the entire range from hyper to anacidity.

The following table gives the colors produced on the papers by gastric contents of different acidities together with the number of cubic centimeters of 0.1 N alkali which would be required to neutralize 100 cc of a solution of the hydrogen-ion concentration found, calculated on the assumption that all acidity in such solutions is due to hydrochloric acid.

Indicator.	pH.	Color.	Cc 0.1 N, NaOH required.	Remarks.
Töpfer's reagent	1.4	Deep red	44	Hyperacidity.
Töpfer's reagent	1.6	Reddish-orange	27	Normal acidity.
Töpfer's reagent	1.8	Orange	17	Normal acidity.
Töpfer's reagent	2.0	Yellowish-orange	10	Hypoacidity.
Thymol blue	2.0	Purple-red	10	Hypoacidity.
Thymol blue	2.4	Faint pink	4	Hypoacidity.
Thymol blue	3.0	Yellow	1	Anacidity.

We have used the procedure outlined above on a great variety of gastric specimens in which we have checked the findings by titration and by the use of the apparatus of Shohl and King.¹ We have also checked our results in a smaller number of cases by means of the electrometric method, and have used for this purpose a Leeds and Northrup potentiometer reading to 0.001 volts, an Epply standard cell, a calomel electrode of standard make, and a Clark electrode with shaker. Just before and just after each series of determinations we have checked our work by carrying out the process on a buffer of known pH content, in order to detect any poisoning of the electrode.

TABLE I.—COMPARISONS OF RESULTS OBTAINED BY DETERMINATIONS OF THE ACIDITY OF GASTRIC CONTENTS OF TEST PAPERS AND BY THE ELECTROMETRIC METHOD.

Specimen number.	pH by test papers.	pH by electrometric method.
1	1.3	1.27
2	1.4	1.40
3	1.4	1.32
4	1.5	1.56
5	1.6	1.64
6	1.6	1.53
7	1.7	1.75
8	1.7	1.80
9	2.0	1.95
10	2.3	2.38
11	2.5	2.43
12	2.7	2.65

As will be seen from the results presented above the agreement between the results obtained by the papers and by the electrometric method is astonishingly close, so that we feel justified in making the statement that after a little practice it should be possible to read these test papers to within 0.1 unit.

Summary. It is suggested that the customary titrations of gastric contents with Töpfer's solution be replaced, at least at the bedside or in the busy clinic, by the determination of the hydrogen-ion concentration by means of test papers, for which the only equipment needed is a small vial of these papers which may be carried in the pocket.

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PERNICIOUS ANEMIA IN ITS RELATIONSHIP TO SPRUE.*

A PRELIMINARY REPORT.

BY EDWARD JENNER WOOD, M.D., D.T.M. (ENG.),

WILMINGTON, N. C.

(From the Clinical Laboratory of the James Walker Memorial Hospital,
Wilmington, N. C.)

FROM the time of its first appearance in medical literature the position of sprue has been unique.¹ Throughout its whole history there have been able clinicians who have refused to recognize it as a distinct clinical entity and it must be admitted that there has been a reasonable basis for such an attitude. Its close similarity to pernicious anemia is a very old observation which seems destined to be repeated in every period. A study of the history of sprue shows that it was an old term before Addison's first report on pernicious anemia, having been accurately described by Hillary in Barbadoes in 1776. As early as 1737, John Brickell, M.D., in his "Natural History of North Carolina" mentioned "white flux" which undoubtedly was sprue.

It is interesting to note how infrequently sprue has been reported out of the tropics. This cannot be explained wholly on the ground of its being strictly a tropical disease because it has been observed repeatedly in this country in northern states among people who have never been in the tropics. Its recognition seems to depend in a measure, at least, on the personal equation of the observer. One experienced in tropical work would readily make such a diagnosis while one without this experience would fit the clinical picture of so-called sprue without reservation in an entirely different classification. An explanation of this state of things will be attempted later in this communication.

Points of Similarity between Sprue and Pernicious Anemia. Sprue first attracted attention in this country when pellagra appeared as a great scourge in the southern states in 1907. Up to that time it had been a rare term in American medical literature and when it did appear it was usually from the pen of some medical officer who had seen service in the Philippines or other tropical post. An exception to this general rule was the experience of Harris,² who found the disease in Georgia. In the South the diagnosis of "pellagra-sine-pellagra" was often made and an investigation not infrequently revealed the fact that the disease conformed to the description of sprue. Such confusion would likely never have existed had the blood-picture been considered. In pellagra there

* Read before the section on medicine of the Medical Society of North Carolina, Raleigh, April 15, 1924.

is no notable blood change while in sprue the rule is that the blood changes are usually as marked and as striking as in pernicious anemia. The term "pellagra-sine-pellagra" soon ceased to appear in the medical literature of the southern states, and justly so, for it became obvious quite soon in the experience with this disease that without the skin lesions or a very definite history of the past occurrence of such a condition the diagnosis was never justified. The diarrhea of sprue and the sore mouth also differed definitely from those conditions in pellagra and a consideration of these symptoms alone was quite enough for a differentiation.

Remissions seem by many to be regarded as not occurring in sprue but in reality they are fully as much a part of the disease picture in sprue as in pernicious anemia, if not, indeed, more so. These remissions are mentioned by all careful students of sprue. The writer has before him the record of one case of sprue diagnosed in 1915 and regarded as a typical case. There was no recurrence of symptoms in this case until 1923 though a careful follow-up correspondence had been applied throughout the whole intervening period. During these eight years there had occurred no symptoms. More recently a case diagnosed as sprue in 1916 returned to a colleague who now diagnoses pernicious anemia with full justification. In this case, however, there had occurred numerous recurrences and exacerbations.

The blood-picture in sprue is strikingly similar to that of pernicious anemia. The color index in every case observed by the writer at some stage of the disease has been over one. The usual range has been between 1.25 and 1.66 and the hemoglobin is frequently between 20 and 30 per cent. The morphology of the red blood cells has been much that of true Addisonian anemia in that there have been found the preponderance of oversized cells, poikilocytosis, anisocytosis, polychromatophilia and to a less extent the occurrence of nucleated red cells. The nucleated cells, as a rule, have been fewer and the occurrence of megáloblasts has been of less frequent record. It must be considered, however, that the search for these blood elements has not been routinely as thorough as in those cases regarded as pernicious anemia.

Among the important points of similarity between sprue and pernicious anemia is the Prussian blue reaction of Perl which occurs when sections of liver are brought in contact with a solution of potassium ferrocyanide and dilute hydrochloric acid. It occurs so infrequently in other conditions that its presence in obscure anemias has been regarded as strong evidence in favor of the pernicious type. It is noteworthy that it also occurs in sprue and in bronzed diabetes. Its occurrence is of more than passing note in this study for it seems to indicate that some hemolytic process has been active as the reaction depends on the presence of hemosiderosis resulting from the deposition of hemoglobin in the tissues after blood destruction.

Study of the bone marrow in sprue has been neglected, judging from the literature. This is true of all postmortem observations in this disease. Even Ashford has had few autopsy opportunities. The writer suspects that this may be explained by the victim of the disease coming to his death with another diagnosis. Bahr (Manson-Bahr)³ describes the bone marrow changes in sprue and gives a table of comparisons between the two diseases. In sprue he found no increase in erythroblastic elements, while in pernicious anemia the characteristic changes were recorded. Very recently Bramwell⁴ has stressed the similarity between the two diseases and thinks that Manson-Bahr's failure to find the evidences of erythroblastic response in the bone marrow in sprue needs further observation and corroboration. He thinks that it is highly probable that in sprue with blood changes so similar to those of pernicious anemia the same alterations in the bone marrow should be expected.

The lack of neurological changes in sprue has been regarded as a point of value in distinguishing between it and pernicious anemia. It is, of course, true that in sprue the nervous system suffers less frequently than in Addisonian anemia but it is an error to assume that it always escapes. The writer has records of a number of cases of so-called sprue which show indications of the usual cord changes of pernicious anemia. Among these cases should be cited that of a Virginia lady who had resided in Porto Rico continuously for eight years. During her last two years in Porto Rico she had been considered by the resident physicians as a case of sprue. Her story indicated for eight months before observation she had been annoyed with sensory disturbances in hands and feet and with some difficulty in walking. Examination revealed loss of sphincter control of both bowel and bladder, loss of the abdominal reflex, presence of the extensor plantar response (Babinski's sign) and exaggerated knee- and ankle-jerks. There was almost complete loss of appreciation of vibration sensation and marked diminution of tactile response in the lower half of her body. Ophthalmoscopic examination revealed old hemorrhagic areas. There were indications of a bulbar lesion affecting speech and deglutition. The diagnosis of subacute combined degeneration of the spinal cord was obvious. The blood showed a high-color index, all the variations in size, shape and staining reaction of pernicious anemia and also the presence of the megaloblast. To these findings was added achylia gastrica. In this case the type of sore tongue and the character of the diarrhea would have justified the diagnosis of sprue while a consideration of the whole case certainly justified the diagnosis of pernicious anemia. It could well be regarded as a typical case of sprue and, on the other hand, there was no single point against the diagnosis of pernicious anemia. One could but feel that the diagnosis was largely a matter of geography. In the tropics it would be called sprue, while out of the tropics it would be called pernicious

anemia. This is by no means an isolated instance of the difficulty and confusion surrounding the whole problem. As the writer's experience with sprue has grown he has become more and more impressed with the difficulty in making this differentiation. Cases seen in the past and diagnosed sprue are returning with every earmark of pernicious anemia, and to somewhat less extent the converse is also true. There are numerous cases in the sprue literature of the disease being complicated by pernicious anemia, of sprue developing into pernicious anemia and of the advanced stages partaking of the nature of pernicious anemia. Certain it is that the symptoms of the one have so merged into the other that a line of demarcation between the two in many instances cannot be drawn.

Achylia gastrica so frequently, if not universally, recorded in pernicious anemia has been regarded as offering a point of differentiation between it and sprue. It seems to be true that in sprue this condition does not occur so universally nor so early in the course of the disease, but the marked difference recorded in the literature is inexact for in sprue achylia does occur and probably much more frequently than one would infer. Its occurrence is later but the writer feels strongly that if the examination were repeated from time to time throughout the course of sprue the absence of free hydrochloric acid would be more frequently recorded. In a case in mind one year before the fatal termination free hydrochloric acid was present but it gradually diminished so that just before death it had disappeared entirely.

It would seem that in this day of laboratory dependence many of the valuable clinical observations of a previous generation are lost entirely or forgotten. One is struck in a review of the early records of pernicious anemia with the frequent references to mouth and intestinal symptoms. A sore mouth is by no means rare in pernicious anemia and the denuded condition of the tongue, the so-called "slick tongue," has been observed by even the casual attendant. The mouth symptoms of pernicious anemia were stressed by Lazarus⁵ years ago. He recorded an extreme sensitiveness of the tongue, the hard palate and the gum. On examination he found on the tip and dorsum of the tongue and on the mucous membrane of the cheek circumscribed reddish areas of a mahogany color which varied in size from a mere point to a dime and which were extremely sensitive and represented areas of hemorrhage into the mucous membrane. In one case he recorded intense painfulness of the tongue and gums at the start of the disease, which lasted for three weeks and developed into severe salivation. This writer also mentions Ewald's observation of a case presenting round vesicles of pin-head size which developed on the tip of the tongue, on its inferior surface and on the mucous membrane of the lips and cheek which left behind a surface desquamated of epithelium. The observations of H. Müller and Laache are also noted in connec-

tion with the observation of excoriation extending in many cases throughout the whole length of the esophagus. One could almost as readily accept these observations as occurring in sprue as in pernicious anemia. Many of the earlier accounts of pernicious anemia are splendid accounts of sprue.

Recently the writer was consulted by two patients solely on account of sore mouth and tongue. Neither presented any other subjective complaint. In both there was an achylia gastrica and in both Ashford's *Monilia psilosis* was recovered. The neurological signs as well as the blood-picture justified a diagnosis of pernicious anemia, but the outstanding significant feature was sore mouth.

The close similarity between sprue and pernicious anemia is of considerable importance, being far more than a simple academic interest. Any investigator working with sprue who is familiar with the clinical manifestations of pernicious anemia must be constantly reminded of the close similarity and probable relationship. It all suggests the question, Is sprue a type of pernicious anemia? Regardless of the attitude one may assume in this matter, the fact remains that the clinician experienced in both conditions will repeatedly meet cases impossible of differentiation.

After this clinical experience it was only natural to apply Ashford's findings of the *Monilia psilosis* in sprue to the problem of pernicious anemia. The results to be recorded below hinge largely on how one regards the work of Ashford. Is the *Monilia psilosis* the cause of sprue or is it in any way connected with sprue? If the *Monilia psilosis* is accepted as the cause of sprue, the work here recorded becomes of great importance. If this work is not accepted, much remains to be done in determining the part the *Monilia psilosis* may play in pernicious anemia. It seems reasonable to assume that the occurrence of this organism in pernicious anemia is something more than a mere accident. Whether or not one accept sprue as a type of pernicious anemia is a matter of the smallest consequence, not at this time regarded as worthy of a controversy as the writer sees it. The evidence of the occurrence of the organism in pernicious anemia is presented as it is and further study and observation must determine its real significance.

Ashford's *Monilia Psilosis* in its Relation to Sprue. In 1901 Kohlbrugge⁶ found in sprue in the intestinal mucus, in the lymphoid patches of the intestinal tract and in the epithelial covering of the esophagus and tongue great quantities of yeasts resembling *Monilia* (*Oidium*) *albicans*.

In 1902 DeHaan⁷ found the same yeast in both acid and alkaline stools.

In 1905 Van der Scheer⁸ reported his inability to find the organism in tongue scrapings or gastric contents in two cases of sprue.

In 1908 LeDantec⁹ found a yeast in sprue stools which would produce sprue symptoms in experimental animals, if a diarrhea was first established in some other way.

In 1909 Macy¹⁰ reported finding a yeast in sprue stools in India.

In 1913 Castellani and Low¹¹ described a number of yeasts which they isolated from sprue stools, but which they regarded as secondary invaders probably only playing the part of producing frothy stools.

The most important work up to 1914 on the part played by yeasts in sprue was that of Bahr (Manson-Bahr)³ in that year. This report was the result of an exhaustive study made in Ceylon. It presents strong evidence for regarding sprue as a blastomycotic infection. Yeasts were found intracellularly in tongue scrapings during the attack, but not at any other time. These yeasts were the only organisms found in the deeper layers of the tongue. There was also found a general infection of yeasts in the intestinal mucosa in sprue, but in no other wasting diarrhea. It is stated that the relapsing nature, the chronicity and the latency are what one would expect from a knowledge of the life history of the blastomyces. This opinion was thought to be reinforced by a consideration of attenuated growth and recrudescences. This observer saw no reason for regarding the organism as any other than the thrush fungus.

Bahr's work was given a new impetus by Ashford,¹² working in Porto Rico. This latter observer spent a decade or longer in an exhaustive study of sprue in relation to a yeast which he named *Monilia psilosis*. It seems probable that this organism was the same that Bahr had studied in Ceylon, but it is not the *Monilia albicans* of thrush as so many seem to think. This organism produces on Sabouraud's medium round, yellowish, glistening colonies; it does not liquefy gelatin; it does not clot nor change the color of litmus milk; it usually produces gas in maltose, dextrose and levulose and occasionally in saccharose and galactose. Ashford will not accept an organism as of the species *psilosis* if it fails to produce gas with maltose. It never produces gas with lactose nor with mannite. The writer has found that if pure sugars are used invariably maltose, dextrose and levulose, and these only, will be fermented with liberation of gas. Until the highest purity sugars were used the results were most misleading. The writer has found it best to grow the organism at 30° C. Ordinarily at this temperature it requires forty-eight hours for a growth visible to the naked eye to appear. The exception to this rule occurs when the organism has been passed through an animal to increase virulence. In this instance the growth is usually more rapid. When colonies appear to the naked eye earlier than forty-eight hours after inoculation, it is reasonably safe to assume that they are not *Monilia psilosis*. Ashford emphasized the importance of an acid medium (as the original formula of Sabouraud designates) and used a +2 titer of decinormal sodium hydroxide with a phthalein indicator. The writer has modified this by making the titer +5 (10 cc of the medium

with a phthalein indicator will then require 5 cc of decinormal sodium hydroxide solution for neutralization). In addition to this decidedly increased acidity the writer has found that this acidity is much better produced with acetic acid than the more generally used hydrochloric acid. In this way the fluidity of the medium after sterilization is prevented and much costly material saved. Through a fortunate accident a batch of medium was burnt on the free flame after the addition of the sugar. It was soon learned that this medium was superior to that not so burnt. The caramelization so increased its good qualities that it is now intentionally resorted to in every instance by heating directly over the free flame. This is done until a definite brown color develops and the smell of burnt sugar is detected. The criterion of a good medium for the work in hand is that when feces is inoculated there will occur no growth on the acid agar-agar slant except of the higher forms and particularly the yeasts. The bacteria must all be completely inhibited and the medium can be so prepared that this can be accomplished without interfering in any way with the development of the yeasts. It has been found advantageous to use media of several degrees of acidity, in order to avoid the inhibition of any organisms which might be important for purposes of study. As a rule the best medium will titrate between +3 and +5 and this is the routine formula. It is expected that by the use of such a medium in general routine work many interesting fields will be opened up, especially in a group of bronchial affections which are non-tuberculous. The yeasts seem destined to play a conspicuous part in the medicine of the future. The development of a culture medium which grows them all readily with a definite inhibition of all bacteria is a step forward.

The Monilia Psilosis in Pernicious Anemia. As stated earlier it is a matter of small moment whether or not sprue is regarded as a type of pernicious anemia. The suspicion that such might be the case led the writer to study the occurrence of the *Monilia psilosis* in the latter disease and after that the graft became so much more important than the original study that this possibly controversial point is left to others more interested. Finding the *Monilia psilosis* in pernicious anemia shifted the scene entirely and relegated the whole subject of sprue to the background.

In 15 cases of pernicious anemia, the *Monilia psilosis* has been found in the feces. Of this number there are only 2 cases about which there can be any diagnostic question and further study is necessary before the disease can be excluded. In something over 40 cases which were neither sprue nor pernicious anemia, the *Monilia psilosis* has not been recovered. In only 1 case of known pernicious anemia has there occurred any difficulty in growing the organism from the feces and this study was made during a period of remission. However, in this case the organism was readily grown

from the pyorrheal gums, a subject to be dealt with later. It has been notable that during remissions the organism is found with great difficulty or not at all in the feces. Speaking generally it can be stated that almost invariably the organism is found in the presence of the disease and equally certainly not found in its absence.

In numerous cases the *Monilia psilosis* has been obtained from cultures made from the gastric contents. It was suspected that possibly the absence of free hydrochloric acid might have been a contributing factor but this was disproved by finding the yeast in the gastric contents before the development of the usual achylia.

Feeding Experiments. In the feeding experiments no attempt was made to render the guinea-pig more susceptible by a faulty diet as had been done by Ashford following certain French investigators. Ashford employed some malted baby food. In the present work the organism was added to the animal's regular diet without any change in the usual manner of living. On the eighth day the first animal died. The source of the organism used was from the feces of a victim of pernicious anemia. Throughout the lungs of this animal were found a few isolated areas suggesting granulomata which seemed to conform with the "white spots" described by Ashford. The blood changes were quite notable in this case. The hemoglobin was reduced from 88 per cent to 62 per cent. There was a considerable preponderance of oversized red blood cells and a striking polychromatophilia. The one thing wanting was an excess of nucleated red cells. The marrow of the long bones presented an intensely red color in sharp contrast to the control animal's marrow. Care was taken to avoid the error of using young guinea-pigs because of the normally more decided red color of the marrow. In the marrow there was an excess of nucleated red cells and an apparent excess of myelocytes. The liver of this animal was sectioned and the Perl reaction applied and found decidedly positive. Again, this reaction was controlled by sections treated in the same manner from a normal guinea-pig. From the feces and gastric contents of the *Monilia*-fed pig the *Monilia psilosis* was recovered. It was notable that in none of the organs was a growth of the yeast obtainable.

The next guinea-pig was fed a *Monilia psilosis* from a case of suspected sprue occurring in the North Carolina Tuberculosis Sanatorium. This particular organism was sent to Colonel Ashford in Porto Rico for his examination and particularly for his opinion regarding the species. He has written that it is unquestionably the *Monilia psilosis* which he has found so universally in sprue. In every way the organism was true to type, which is not universally true of this class of yeasts. It produced gas in the fermentation tubes with maltose, levulose and dextrose. Litmus milk remained unchanged and gelatin was not liquefied. This organism was fed to a guinea-pig as a simple addition to its previous diet. For a time

no symptoms were produced and it was assumed that the organism from long incubator life had become attenuated. Consequently in order to render it more virulent passage through a rabbit was resorted to with death of the animal in forty-three hours after the intravenous inoculation. Autopsy of this rabbit revealed no gross changes, but the *Monilia psilosis* was recovered in pure culture from the liver, kidney stomach and feces. This new culture was then substituted for the old one and the feeding continued. After a few days the guinea-pig being thus fed died and the same changes that had been found in the first animal which had been fed a culture from the feces of pernicious anemia were again found. Notably the bone marrow of this animal showed great numbers of myelocytes chiefly of the neutrophilic variety and a definite excess of nucleated red cells. The color of the bone marrow was a brick-dust red, though it was from an old animal, and it was quite gelatinous in its consistency. The blood cells showed a very great variation in size with a marked excess of over-sized cells. There were definite variations in staining reactions and marked poikilocytosis. This animal showed the characteristic changes probably more definitely than did the former animal. In the lungs and liver there occurred a few of the granulomatous areas mentioned above and the changes generally were enough to justify the conclusion that the two processes were one and the same.

A third guinea-pig was fed a *Monilia psilosis* recovered from a fatal case of pernicious anemia. Until after the feeding had progressed several days, it was not known that this animal was pregnant. The feeding was discontinued until the young pigs were two weeks old, when it was resumed. In all six weeks feeding-time was required to cause death. Before death there was marked emaciation and loss of hair. At autopsy the bone marrow was deep red and gelatinous. The liver, and to less extent the kidneys showed a marked reaction to the Perl test. The cholesterol content of this animal's blood was 107 mg. per 100 cc of blood. The red blood cells showed definite megalocytosis and polychromatophilia. The young of this animal died a few days after the mother's death. These animals had not been fed the yeast, but had lived in the same case with the mother. Cultures from the intestinal tract of both the young animals showed the *Monilia psilosis*.

Intraperitoneal injections of the *Monilia psilosis* in white mice caused peritonitis but the tardiness of the onset of symptoms and recovery in some instances indicated that the animal was peculiarly resistant or else that the yeast was of low virulence.

All of the culture work on many animals fed this yeast showed that it was not a blood-stream invader except when injected intravenously. Given by mouth, it will eventually kill, but the time required varies greatly with different cultures, as would be expected. Growth on artificial culture media soon renders the organism less virulent and the longer the artificial growth the greater the loss in

virulence. The virulence is readily raised by passage through one or more animals. It seemed reasonable to assume from this work that the organism in the intestinal tract elaborated toxins which when absorbed prove to be hemolytic in nature.

The *Monilia psilosis* was next grown in dextrose water. The strength of the dextrose solution varied from 4 per cent to 20 per cent. The culture was incubated at 30° C. for five days and then filtered with great care to prevent any contamination. The filtrate was given intravenously to rabbits, after cultures had proven it to be sterile. The amount of the initial dose was 1 cc, which was repeated daily with a continuous increase in the size of the dose. The organism used in the first of this group of experiments intravenously had killed a rabbit in forty hours with a mycotic septicemia. The filtrate had no such effect. On the fifth day the rabbit receiving the filtrate was examined and the blood showed early changes. On the tenth day the blood showed numerous nucleated red cells which had formerly been absent and some of these cells were of the megaloblastic type. The hemoglobin was lowered 15 per cent. The red cells showed many variations in size and also poikilocytosis. The polychromatophilia present was of no significance for, as is well known, this is a normal finding in rabbit's blood. These blood changes could hardly be regarded as any other than those of a hemolytic anemia. After these definite changes had been produced the inoculations were discontinued and the animal's blood promptly returned to its original normal.

SOURCE OF THE *MONILIA PSILOSIS* IN THE INTESTINAL TRACT. The question then arose, Where does this yeast come from and how does it reach the intestinal tract? Ashford in his sprue work in Porto Rico suspected the yeast-risen bread of the natives because from the center of the loaf he had secured cultures of the organism. This, however, could not explain the freedom from the disease in little children, who consume as much as or more bread than the adult. All of the available evidence strongly suggested that the organism was swallowed. After becoming satisfied that faulty cookery was not responsible for the infection, the writer reverted to the question of oral sepsis which W. Hunter had suggested in his work on the severest anemias. He had suspected a streptococcus as the cause, but this view had not been sustained. With this in mind, cultures were made from the gums in pyorrhea. The cases selected for this were victims either of sprue or pernicious anemia. Without difficulty the *Monilia psilosis* was readily grown and there has not occurred since that time a case of either of these two conditions in which there has been a failure to secure a growth of the organism from this source, except, of course, in those patients whose teeth have been removed and the gum has healed. It will be recalled that during periods of remission in pernicious anemia it has frequently been difficult, if not impossible, to secure a growth from the feces but from the gums the cultures have been consistently

positive. Cultures from the roots of extracted teeth at the time of removal have invariably proven negative. With a culture derived from the gums the hemolytic changes were produced when the filtrate was employed. Many controls of this gum work have been done and there are surprisingly few instances of a positive culture, regardless of the degree of pyorrhea existing. There have been some cases giving a positive response when there were no other evidences of disease, but this was to be expected. It would be as absurd to expect that every patient with the *Monilia psilosis* in the mouth was the victim of a grave blood disease as to regard every positive culture of a hemolytic streptococcus from the mouth as of clinical significance.

Summary. 1. The close similarity of pernicious anemia and sprue suggests the possibility of the two being types of the same condition.

2. Equally as readily in pernicious anemia as in sprue, the *Monilia psilosis* can be recovered from the feces, the gastric contents and the gums when pyorrhea exists.

3. The study of the yeasts is made extremely simple by the employment of a modification of Sabouraud's medium.

4. By feeding guinea-pigs with the *Monilia psilosis* a hemolytic anemia was produced. There were also produced changes in the liver and bone marrow which were suggestive of the action of a hemolytic poison.

5. A filtrate of the *Monilia psilosis* in dextrose water injected intravenously into rabbits caused blood changes apparently hemolytic in nature.

In conclusion the writer wishes to express to his friend, Dr. Thomas M. Green, his appreciation of his encouragement and kindly criticism. To Miss Lila W. Koonce, technician in the clinical laboratory of the James Walker Memorial Hospital, he offers his thanks for invaluable aid throughout the work.

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OBSERVATIONS AFTER TEN YEARS ON A SERIES OF CEREBRO- SPINAL SYPHILITICS TREATED BY INTRAVENOUS AND INTRASPINOUS THERAPY.

BY GEORGE DRAPER, M.D.,

NEW YORK.

IN 1915 I¹ published a series of cases of cerebrospinal syphilis which had been treated after the manner of Swift and Ellis,² over a period of from six months to two years. The results of this short course of treatment were most satisfactory, and may be found fully described in that original paper; but because this was a new method of treatment it was impossible to foretell what the subsequent results would be.

Ten years have now passed since those initial improvements were experienced by this group of patients, and it seemed that it would be not only interesting but instructive to observe what has happened since. Ten years is a long time through which to maintain satisfactory contact with a large group of patients and it is inevitable that a certain number should be lost sight of. This fact renders the absolute statistical value of such a review unsatisfactory. There are, however, enough observations available on this group of patients to be of value.

The material on which this communication is based may properly be divided into two portions. One, composed of the 25 which formed the original group reported in 1915, and the other later collection of 20 cases, which have been observed for a somewhat shorter period. Now, of the original group of 25, 9 or 36 per cent have disappeared; 7, or 20.8 per cent are dead; 9 or 36 per cent are living, practically in almost all cases free from symptoms and with 2 exceptions actively at work. One of the individuals who is not actively at work is physically and mentally quite capable of working but, without the pressure of necessity, prefers to remain inactive.

The following table shows the detail of the spinal fluid and serological formula of each case at the time of admission to treatment, at the time of discharge at the end of treatment, and again at the end of the ten-year period. A perusal of the table will show that the gain achieved at the end of the treatment period has in all cases not only been held but in numerous instances to a surprising degree has been bettered. Such physical signs as the Argyl-Robertson pupil, absent reflexes, and marked disturbances of skin sensation have not changed, perhaps because such signs depend on actual destruction of nerve tissue. But the subjective symptoms, such as pain, gastric distress, weakness and, especially, irritability and lack of mental poise have improved during the six to nine years

Case No.	Diagnostic data.						Discharge data.							
	Spinal fluid.				Blood W.R.	Duration of treatment, mos.	Number of intra-venous.	Number of intra-spinal.	Spinal fluid.				Blood W.R.	Condition.
	Cells.	Glob.	W.R.	Gold.					Cells.	Glob.	W.R.	Gold.		
49	25	=	0.5	0	-	9	10	0	1	--=	0.5	0	-	Marked improvement; fixed pupils K. J. -
126	138	+	0.1 +++++	0	++	4	9	5	0	++	0.5 +++++	1233- 2100	=	Gastric crises stopped; general improvement; fixed pupils K. J. -
76	40	+	0.3	0	+++	5	17	5	1.2	=-+	0.5	0	++	Pain gone; ataxia better; fixed pupils K. J. -
95	51	+	0.5 +++++	0	Not done +++++	7	21	3	10	++	0.5 +++++	0	-	Ataxia-irritability; pupils sluggish K. J. -
96	133	+++++	0.3 +++++	0	+++++	3	10	5	6	++	-	0	-	Slight improvement; complete ataxia K. J. -
91	53	+	0.5 ++	0	-	6½	10	0	15	=-+	-	0	-	Improvement in visual field and general health. Patient apparently well.
22	52	+++++	0.3 +++++	0	++	9	24	12	10	-	0.5 =	1112- 161	-	Patient apparently well.
18	40	++	0.1 +++++	0	+++++	4	11	9	23	-	0.5 +++++	0	++	Patient apparently well.
25	327	+++++	0.5 +++++	0	+++++	9	22	15	33	++	0.3 +++++	0	+++++	Marked improvement in all symptoms.

Ten-year data.

Case No.	Spinal fluid.				Blood W.R.	Condition.	Time, yrs.	Without symptoms.
	Cells.	Glob.	W.R.	Gold.				
49 126	... 2	... +	... 2.0 —	... 112321000	... —	No pain at all; fixed pupils K. J. — Complete subjective comfort and efficiency; fixed pupils K. J. —	6 8	Well; active. Mercury and 7 Ogilvie intra-spinous; well; active; severe arsenic dermatitis. Comfortable; not active.
76						Continued absence of pain; ataxia slight; pupils and K. J. same	9	Well; slight ataxia; active.
95	3	0	2.0	11121100	—	Ataxia improved; irritability gone; physical signs the same	6½	Feels well; very ataxic.
96						Ataxia improved; bladder control less good; general condition excellent	8	Eyes stationary; well; active. Well; active.
91 22 18 25	3 0 2	— — —	— — —	343321000 ... 1222100	— — —	Held eye gain; fine general health Patient apparently well Patient apparently well Continued improvement in strength and psychic poise	8 8 8 9	Perfectly well; active. Well; active.

in which these patients have lived without treatment. Two or 3 of the cases, it is true, have received, about midway between the cessation of the original series of injections and the present, a short course of treatment. But several who have received nothing have steadily improved in physical well-being and psychic demeanor.

In the original communication the cases were arranged according to their outstanding symptoms. Thus there was a pain group, an ataxia group, an optic atrophy group, a single case of cranial nerve nucleus involvement, and the psychic disturbance group. Of the 9 cases who have done well, 3 were from the painful group, 2 from the ataxic, 1 from the optic atrophy, the bulbar case, and 2 from the psychic group. In the original spinal fluids the cell counts of these 9 cases ran from 25 cells to 327 per 1 cm. At the end of treatment the cells varied from 0 to 33 cm. and at the end of the ten-year period from 0 to 3. The Wassermann reaction, which was strongly positive in all the fluids at the start and which at the end of treatment was not completely negative, at the end of the ten-year period was negative throughout. The globulin reaction followed a similar course. No colloidal-gold reaction was done on the original fluid because the test had not been devised at that time, so that while in a few instances, subsequently, fluids from this series were tested by the Lange method, the observations are not sufficiently consistent to warrant a comparative report. It may be said, however, that in the ten-year spinal fluids the gold reaction shows a very slight change of the luetie type in all the fluids examined. The blood Wassermann reaction was strongly positive in the original test, incompletely eliminated at the end of treatment, but at the end of ten years was negative in every one. Obviously, then, there has been during these intervening years a continued improvement, not only in the physical well-being and relief from pain and specific disability, but also an almost complete clearing up of the disturbed formulæ.

Before entering upon a discussion of the inferences to be drawn from these results, it would seem desirable to consider for a moment the other group of 20 cases which have been treated in precisely the same way and during almost as long a period. Of these 6 or 30 per cent have disappeared, 2 or 10 per cent are dead, 7 or 35 per cent are well and active, 5 or 25 per cent are worse. Of these last 3 turned paretic during or after months of treatment; 1 was already a fully developed paretic when treatment was begun and 1 was an extremely painful ataxic who after a long period of amelioration went steadily and rapidly down hill. Thus it appears that the number of those who are able to be comfortable and work actively is practically the same in each group. But in this last group there are certain striking individual cases which are so important for the purpose of rounding out my conception of the therapeutics of this disease that it is necessary to give brief histories of them. Three of

them represent failures; 1 a questionable or perhaps accidental success.

CASE I.—W. T. C., male, telegrapher, aged fifty-two years, complained chiefly of loss of vision. In November, 1916, the patient could see enough to work but his visual fields were very much contracted. There were absolutely no other symptoms or signs. His spinal fluid formula at that time showed 6 cells, globulin 1 plus, Wassermann reaction positive in 0.1 cc, gold-chloride reaction 5555554210. The patient received 15 intravenous injections and 10 intraspinal up to February, 1918. His eyes held their own during this period. He then went without treatment, apparently perfectly well until the summer of 1922, when without warning he suddenly developed active paresis. His spinal fluid showed precisely the same formula as it had in November, 1916. This case is particularly striking because of the absence of any mental or bodily symptoms or signs save the localized optic atrophy.

CASE II.—W. C. C., lawyer, aged forty-six years, complained chiefly of numbness over the buttocks, through the crotch, and down the backs of the thighs. The spinal fluid formula was: 41 cells, globulin 4+, Wassermann reaction 4+ in 0.3 cc. Treatment was begun in February, 1915. At the end of the first year, the patient had received 29 intravenous injections of salvarsan and 14 intraspinal injections of serum, as well as a considerable number of injections of mercury. The spinal fluid formula at this period showed 3 cells, globulin 1+, Wassermann reaction 3+ in 1 cc. Gold chloride 111332000. The subjective symptoms were practically gone, patient felt and seemed perfectly well. During the next nine months, however, he received 2 more intraspinal treatments and in October, 1917, the fluid had relapsed, showing 45 cells, Wassermann positive in 0.4 cc; gold reaction 22342100. The patient was then given 4 intravenous treatments and 10 intraspinal, after which the spinal fluid showed a gold curve of 5554421000. Nevertheless he remained well all through the summer of 1918. In January, 1919, he was still free from clinical symptoms but the spinal fluid showed 30 cells, globulin 3+, Wassermann reaction positive in 0.4 cc and a Lange test of 5555443210. He received 3 intravenous and 4 intraspinal injections which was followed by a general improvement in health throughout the year. Beginning in February, 1920, he received 5 intravenous treatments each followed by a spinal puncture but no injection of serum. At the end of this course the spinal fluid still showed 33 cells, 3 plus globulin, a complete fixation in 0.4 cc and a gold curve of 5555554211. Shortly after this spinal fluid formula appeared, the patient expressed great worry lest he lose his mind. He was reassured with the statement that people who were in fear of losing their minds rarely did so and

at all events never themselves recognized the moment of mental change. He expressed particular worry over the fact that he could not sleep and that the loss of sleep was pulling him down. Two weeks later he said to me with just a suggestion of exaggeration in his tone, "Well, now I am perfectly all right; I am not sleeping at all, but I am so well that it does not make any difference. I feel splendidly." The subtle change had taken place. The euphoria of clinical paresis had begun. The point of particular interest about this case is the steady advance of the disease in the face of prolonged and vigorous treatment.

CASE III.—M. B., jeweler, aged thirty-two years, complained only of incessant headache.

In May, 1914, the patient is reported to have had a cell count in the spinal fluid of 500, but the first fluid in this series of observations showed 11 cells, globulin 2+, and Wassermann reaction 3+ in 0.3 cc. No gold reaction was done at that time. The patient was given 21 intravenous and 14 intraspinal injections with some temporary relief from the headaches. Another series of 18 intravenous and 10 intraspinal produced a very considerable relief from the headaches and the last spinal fluid showed 13 cells, negative Wassermann reaction, but a gold-chloride curve of 223321000. Again after a short period his headaches began again. Two years later he became paretic.

These 3 cases illustrate the interesting condition in which individuals complain of a single rather isolated symptom. Except for this one disability, they had no other somatic or psychic indication of the disease. They all showed spinal fluid and serum changes. In the face of the most intensive and prolonged treatment all three turned paretic.

CASE IV.—G. A., aged forty-one years, a business manager, came for advice because he was worried lest he develop locomotor ataxia having been treated for syphilis many years ago. There are no physical signs indicative of central nervous disease, the patient has a perfectly clear and well poised psyche, and has no symptoms. The blood Wassermann reaction was 4+; spinal fluid cells, 105; globulin, 3+; Wassermann, 4+ in 0.4 cc; gold reaction, 553421000. During the last two months of 1916 and for the first six months of 1917 the patient received mercury injections, salvarsan injections and a few intraspinal injections. At the end of this period his cell count was 7 cells, Wassermann was positive in 0.4 cc, and the gold curve was 5334421000. The patient then appeared to be as well as ever and did not return for any treatment until 1922 when he came back in response to a follow-up letter. He appeared to be in perfect health in every respect with the possible exception of getting tired more easily than in the past. There were no physical

signs indicating central nervous disease. The spinal fluid showed 102 cells, positive globulin, Wassermann in 0.4 cc, and Lange curve 123444210. The patient was immediately put on a course of treatment and during the past eleven months has had 30 intravenous injections and 13 intraspinal. His spinal fluid today shows 1 cell, negative globulin, Wassermann incomplete fixation in 2 cc and Lange gold curve 1112332100. The patient is still without symptoms.

Here then is an individual who presented eight years ago the interesting paradox of complete freedom from any signs or symptoms of central nervous system disturbance in the presence of a fully developed parietic formula in the spinal fluid and blood. Under treatment the spinal fluid formula was very definitely modified toward the normal, but without any apparent effect upon the patient's general health which remained as good as it had been before. Then, after a period of four years without treatment and while feeling practically well, the patient returned with a fairly active syphilitic meningitis spinal fluid formula. If it had not been for the follow-up letter, this patient would undoubtedly have gone on indefinitely without consulting a doctor. In view of this finding, it is interesting to speculate as to what has become of the 9 disappeared cases in the first group and the 6 disappeared cases of the second group. One cannot escape the thought that some of these individuals likewise may have developed a rapidly advancing paresis or syphilitic meningitis at the end of a two- or three-year period of apparently good health.

Now, if we consider all this material together two fundamental facts appear. One is, the difference in the severity of the disease expressed usually in terms of disproportion or lack of relationship between clinical symptoms and serological changes. The other is the different manner in which various individuals respond to treatment. If salvarsan and salvarsanated serum are specifics they should cure every time, unless there be another factor involved. The obvious inference from these observations is that the factor which determines the differences in intensity of the disease and the differences in response to therapy is one and the same, namely, the variable factor of individual constitution. There is undoubtedly still a third but minor influence present and that is the period in the disease at which the case appears for treatment. Obviously, then, the ideal therapeutic combination for the treatment of cerebrospinal syphilis is that of a specific spirocheticide and a specific resistance elevator. So much has been written about the specific spirocheticides that it would seem unnecessary to discuss them again at this time, but it may be worth while to consider for a few moments the possibilities that exist for raising to a higher level the specific resistance of the individual.

There are many observations recorded by clinicians of every age

concerning the relationship of certain types of mankind to certain diseases. Naeké³ pointed out some sixty or seventy years ago that individuals who developed locomotor ataxia belonged to what he called the "hoch wuchs," asthenic type, whereas the parietic was a "breit wuchs" or thick set, broad-faced individual. In 1917 I reported a series of cases of cerebrospinal syphilitics studied from the standpoint of their body conformation and found the same situation as that described by Naeké. Such observations as these lend support to the conception of specific resistance-lacks. These specific resistance-lacks must undoubtedly depend upon characters in the individual constitution. Without entering at this time upon a discussion as to the mechanism which determines the constitutional differences in human beings, we may properly recognize the fact that attempts have been made throughout the history of medicine to correct these inadequacies of resistance. The simplest example of this sort of therapeutics is the fresh air, overfeeding and rest treatment of tuberculosis. But there have been other, much less obvious, and indeed totally unexplained phenomena of resistance elevation, often as a result of the most unexpected influence. Perhaps one of the most spectacular of these was the effect of crysipelas and the bacillus prodigiosus in raising the resistance in certain forms of sarcoma as pointed out by Coley.⁴ The recent much talked of cure of paresis by inoculation with living malaria germs may very well be another example of this sort. The new pentavalent arsenical "tryparsamide," which was employed so successfully by Louise Pearce⁵ in African sleeping sickness, in all probability, influences the disease beneficially through its effect on the constitution of the individual.

To anyone who has had the opportunity of observing the extraordinary change in general health and indeed of the entire personality which occurred in the cases of the first group of this series, it must become apparent that the change in the individual goes far beyond the simple return to a symptom-free state due to the destruction of the spirochete.

Conclusion. The Swift-Ellis method of treatment undoubtedly is very effective in a certain type of case, representing, according to this small but varied series, about 36 per cent of all cases of cerebrospinal, or central nervous syphilis.

Successful results of the treatment of cerebrospinal syphilis do not depend alone upon the spirocheticidal effect of salvarsan and mercury, there is undoubtedly some other factor developed in the course of the treatment, which successfully raises the resistance of the individual. When this resistance elevator fails to develop, no amount or intensity of treatment with salvarsan, serum and mercury can check the destructive advance of the disease.

In view of the tendency to recrudescence, all apparently cured

cases should be instructed to report for physical examination and spinal fluid test every two years and possibly oftener.

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VOLUME AND COMPOSITION OF THE BLOOD IN ADDISON'S DISEASE.

BY GEORGE E. BROWN, M.D.,

AND

GRACE M. ROTH,

TECHNICAL ASSISTANT,

DIVISION OF MEDICINE, MAYO CLINIC, ROCHESTER, MINN.

ADDISON, in his original description of the constitutional and local effects of disease of the suprarenal capsules, called attention to the following characteristic features of this condition: "anemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach and a peculiar change of color in the skin." At the time these observations were made, quantitative methods for the estimation of the hemoglobin and erythrocytes were not available. The appearance of the skin and mucous membranes in many cases is such that a severe grade of anemia is often suggested, particularly in blond persons and in those with a mild degree of pigmentation, which gives the skin a light brownish sallow tint. In other cases, there is no suggestion of anemia because of the extreme degree of pigmentation, although the mucous membranes, by contrast, appear to be paler than normal. Since Addison's complete description of this interesting condition appeared, numerous observations have been made, both from the clinical and laboratory standpoints. The question of the blood findings has been considered by a number of workers, with some diversity of opinion relative to the existence of anemia. The comparative rarity of this disease may explain this fact in some degree.

Literature Relating to Composition of the Blood. Auerbeck² asserts that anemia is present with a reduction of the total blood volume, which masks the exact degree of anemia. Buhl⁴ holds that there is a quite uniform, sharp decrease of blood cells, while Tschirkoff¹⁷ made interesting observations in 2 cases in which he noted a daily fluctuation in the whole amount of hemoglobin, as well

as the proportion of oxyhemoglobin to reduced hemoglobin. Neumann¹⁰ observed 1 case in the acute stage of Addison's disease in which low erythrocyte values (1,120,000 for each cubic millimeter) were obtained. Following clinical improvement, a progressive increase in erythrocytes was observed. Nothnagel^{11, 12} believes that anemia is not a primary symptom of Addison's disease. He found average normal hemoglobin and erythrocyte values in uncomplicated cases. Hamel⁸ says that in cases of Addison's disease with anemia and morphologically normal blood, tuberculosis of the suprarenals is probably associated. If anemia is accompanied by morphologically disturbed blood, carcinoma of the adrenal should be suspected. Dock⁶ found average normal blood values in 4 cases, and concludes that anemia is not an essential feature of Addison's disease. Osler¹³ says that anemia is not common, the blood counts being normal in the majority of cases. Several observers have called attention to a high relative lymphocytosis in this condition, to which finding a prognostic value was assigned.

On account of this diversity of opinion with regard to the incidence of anemia in Addison's disease, and since a rather large number of cases had been observed in the Mayo Clinic during the last two years, it was considered advisable to study the blood findings in these cases. It seemed possible that many of the diverse quantitative data with regard to the blood, noted by different observers, might be explained on the basis of fluctuations in the blood volume; therefore, the percentage hemoglobin and erythrocyte counts were correlated with the blood-volume values obtained by a method of reasonable clinical accuracy.

Seventeen cases of Addison's disease, all typical except one (Case XVII), were studied.* Three cases came to necropsy when definite lesions of the suprarenal glands were found. Case XVII presented features of unusual interest. The patient had syphilis, and, following arsphenamin injections, a group of symptoms developed closely approaching that observed in true Addison's disease: asthenia, low blood-pressure, and definite pigmentation. The pigmentation was especially noticeable on the tongue and mucous membranes of the mouth. Following the Muirhead treatment, as outlined by Rowntree,¹⁵ marked improvement followed, which has persisted for two years. The exact status of this case is not quite clear. We believe that disease of the suprarenals existed in which compensation was disturbed by the arsenical treatment. A syphilitic lesion of the suprarenal bodies was suspected.

Terminology. There is no group of terms which designates the various states of blood volume and the different cell-plasma-volume ratios. To supply this need, the following terms have been suggested:³ Normovolemia for normal blood volume, hypervolemia

* The study of the blood in this series of cases, correlated closely with the data in a larger series reported from the Main Clinic.¹⁶

for increased blood volume, and hypovolemia for decreased blood volume. To designate the different cell-plasma-volume ratios, the following qualifying terms may be used as prefixes: Simple for normal cell to plasma-volume ratio, polycythemic for increased cell to plasma-volume ratio, and oligocythemic for decreased cell to plasma-volume ratio.

Treatment. In 11 cases the full Muirhead treatment was used. In Cases VI, XV and XVI, in which a shock-like state was present, the treatment consisted of forced fluids, glucose and stimulants. There was a marked intolerance to the treatment with epinephrin in Case VI.

Findings. The hemoglobin was 70 per cent by the standard Dare method, and 90 per cent or less by the Haldane-Palmer method, and the erythrocytes numbered 4,000,000 for each cubic millimeter or less in 6 cases (37 per cent, Table I). There was borderline anemia in 2 cases. The patient in Case IX, who had the most marked degree of anemia, died within three days. Four of the 6 patients in whom the anemia was fairly definite died within a month. Except in Case IX the anemia, when present, was mild. There were no instances in which there was a high percentage of hemoglobin or high cell counts except in Case VI, during the shock period of acute suprarenal insufficiency. Subsequent examination of the blood showed this to be transient and definitely associated with the shock condition. Considerable variations in hemoglobin and erythrocyte values, seemingly too great for errors of method, were observed in several cases for short periods. The repeated volume studies in several cases seem to show that the percentage hemoglobin variations may be related to shifts in plasma and cell volumes.

Volume and Hemoglobin of Erythrocytes. The volume index of Capps,⁵ or volume of the red cells as compared with normal, and the saturation index of Haden,⁷ or relative amount of hemoglobin in the cell as compared with normal, were determined in 5 cases. The color index, average volume of the erythrocytes and hemoglobin content of individual cells is shown in Table II. The hemoglobin values are expressed in percentages according to Haldane's and Haden's normal standards, 13.8 and 15.6 gm. of hemoglobin for each 100 cc of blood for both sexes, respectively. The normal color, volume and saturation indexes are 1. The normal volume of the average cell, according to Haden, is 9.2×10^{-11} cc. The average normal hemoglobin content of the average cell in both sexes is 3.12×10^{-11} gm. The actual percentage of hemoglobin in the average erythrocyte is 33.9. In this series of cases of Addison's disease, the color index was less than 1 in 3 instances, the average being 0.9. The volume index was 1 or less in all cases. In Case III, a volume index of 0.78 with hemoglobin of 105 per cent was observed. In Case V a volume index of 0.82 was found with a percentage of

TABLE I.—BLOOD STUDIES IN ADDISON'S DISEASE.

Case.	Date.	Hemoglobin per cent.		Erythrocytes.	Leukocytes.	Polymorpho- nuclears, per cent.	Lymphocytes, per cent.	Mononuclears, per cent.	Transitionals, per cent.	Eosinophils, per cent.	Basophils, per cent.	Remarks.
		Dare.*	Palmer									
1 (A 403755)	9-8-22	70	64	4,000,000	6,000	Typical case; patient improved.
2 (A 401101)	9-12-22	73	72	4,380,000	11,200	Typical; patient much improved.
3 (A 407966)	10-17-22	80	105	4,700,000	8,700	48.0	34.5	4.5	5.0	6.0	1.5	Typical.
4 (A 59466)	4-21-23	77	105	4,610,000	7,200	52.0	39.0	2.0	3.0	4.0	...	Typical; patient much improved.
5 (A 433553)	4-24-23	80	111	4,980,000	8,700	58.5	24.5	4.5	5.0	6.0	1.5	Typical; patient much improved.
6 (A 291269)	7-19-23	67	...	3,750,000	6,000	36.0	54.5	1.5	3.5	4.0	0.5	Typical; patient died one month later.
	8-15-23	69	82	3,920,000	5,200	25.0	62.5	5.8	2.5	4.0	0.5	Clinically typical; patient died seven days later. Necropsy revealed chronic caseous tuberculosis of suprarenals and lungs.
	7-3-23	78	154	5,260,000	8,900	64.0	30.0	3.0	1.0	1.0	1.0	Clinically typical; patient died twenty days later. Necropsy revealed marked suprarenal atrophy. Old tuberculous pleuritis.
7 (A 426922)	7-15-23	85	112	5,440,000	During shock period		Clinically typical. Chronic tuberculosis of kidneys. Patient died six months later.
	5-22-23	104	7,600	Patient died three days later. No necropsy.
	5-28-23	78	...	4,880,000	7,200	Typical case; patient died one month later.
	5-30-23	78	111	4,850,000	7,200	Clinically typical. Necropsy revealed bilateral tuberculosis of both suprarenals.
	6-7-23	78	119	4,850,000	...	48.5	46.7	3.0	...	1.0	1.0	Typical; patient improved.
8 (A 232618)	7-17-20	7,600	Typical.
	7-31-20	68	...	4,380,000	9,200	46.5	30.5	4.5	2.0	3.8	3.0	Typical.
	8-2-20	76	...	5,100,000	9,200	60.5	30.5	4.5	2.0	1.5	1.0	Typical; patient died one year later.
9 (A 411539)	11-20-22	53	...	3,280,000	8,600	64.0	26.0	2.0	4.0	3.0	...	Typical.
	12-1-22	50	...	2,960,000	6,400	60.0	52.0	3.5	...	2.5	...	Typical; patient died one month later.
10 (A 390936)	5-9-22	70	...	4,090,000	17,100	64.0	52.0	3.5	...	3.0	...	Clinically typical. Necropsy revealed bilateral tuberculosis of both suprarenals.
11 (A 352505)	3-15-21	67	...	4,020,000	13,800	40.0	43.5	8.0	...	6.0	2.0	Typical; patient improved.
12 (A 428040)	2-26-22	68	...	3,950,000	12,400	40.5	43.5	2.0	...	3.5	2.5	Typical.
	6-6-23	76	...	4,440,000	8,000	51.5	40.0	2.0	...	Typical.
	6-7-23	76	101	4,440,000	...	49.5	45.0	1.0	2.5	2.0	...	Typical.
13 (A 400254)	8-16-23	67	77	4,210,000	11,300	49.5	45.0	1.0	2.5	2.0	...	Typical; patient died one year later.
14 (A 385612)	8-23-23	73	...	4,280,000	13,800	42.5	50.0	4.5	...	2.5	...	Typical.
	3-7-22	71	...	4,040,000	6,800	42.5	50.0	4.5	...	2.5	...	Typical.
15 (A 458373)	3-14-24	75	106	4,830,000	10,000	34.5	54.0	2.0	1.0	2.5	0.5	Typical.
	3-22-24	75	106	3,920,000	9,200	52.0	46.0	...	2.5	2.0	...	Typical; patient died April 8, 1924.
16 (A 459172)	3-21-24	72	92	4,690,000	6,600	70.0	28.0	2.0	Typical.
Average values	72	100	4,420,000	9,040	48.0	40.5	3.2	2.8	3.2	1.7	Typical; patient died April 8, 1924.

* Standard: Dare.

TABLE II.—VOLUME AND HEMOGLOBIN CONTENT OF THE ERYTHROCYTES.

Case.	Erythrocytes.	Hemoglobin.				Hematocrit cells, per cent.	Color index.*	Volume index.*	Saturation index.*	Volume average cells in cc $\times 10^{-11}$	Gm. hemoglobin in average cell $\times 10^{-11}$	Actual per cent hemoglobin in cells.	
		Gm. for each 100 cc of blood.	Normal, per cent.		Haldane scale.								Haden scale.
			Haldane scale.	Haden scale.									
1	4,000,000	8.8	64	57	33	0.7+	0.98	0.73	8.25	2.21	26.7		
2	4,700,000	14.5	105	93	43	0.1	1.08	0.91	9.15	3.08	33.5		
3	4,610,000	14.5	105	93	30	1.0	0.78	1.29	6.50	3.10	47.0		
5	3,920,000	11.3	82	73	27	0.9	0.82	1.13	6.90	2.80	40.0		
7	4,850,000	15.3	111	98	41	1.0	1.00	1.01	8.40	3.10	37.0		
Average	4,410,000	12.8	93	82	35	0.9	0.93	1.01	7.80	2.80	37.0		

* Based on Haden's normal hemoglobin standard.

hemoglobin of 82. The average volume index for the 5 cases was 0.93. The saturation index was less than 1 in Cases I and II, while the average for the group was 1.01. The average volume of the individual erythrocyte was decreased in Cases III and V, and the average volume for the group was 7.8×10^{-11} cc. The average content of hemoglobin in the cell was 2.8×10^{-11} gm. while the percentage of actual hemoglobin for each cell was 37.

According to these calculations, the red cells in 5 cases of Addison's disease showed a decreased cell volume with an increased saturation index as compared with Haden's values, and increased percentage of hemoglobin for each cell. In Cases III and V the relatively high percentage of hemoglobin with relatively low percentage of cells by hematocrit can be explained by a small cell volume with high content of hemoglobin.

Leukocytes. There were no striking variations in the number of leukocytes for each cubic millimeter of blood. Mild leukocytosis was present in 5 cases; in the remainder the counts were fairly normal. The average for the entire series was 9,040 for each centimeter of blood. The differential formulas verify previous observations on the presence of a relatively high lymphocytosis. In this series, the relative value of lymphocytes was increased in 11 cases or 68 per cent, the average percentage value for the entire group being 40.5. In no instances were low relative values found. The relative lymphocyte counts apparently had no prognostic value. The polymorphonuclear cells were relatively decreased in every case, the average values for the series being 48 per cent.

Blood and Plasma Volumes. Blood-volume changes in Addison's disease have been suggested as a possible explanation for the absence of anemia. It is conceivable that an actual decrease in the circulating hemoglobin or erythrocytes might be partially masked by a shrinkage in the total blood volume. Percentage hemoglobin values would not accurately reflect the true condition. With this point in mind, volume determinations were made by the dye method in a series of 9 cases in which the clinical diagnosis was Addison's disease. According to body weight, the total circulating blood volume revealed normal relative values, normovolemia (Table III) in 8 cases. In 1 case (Case V) there was decreased relative blood volume, but it was still within the normal range. In Case II, with average body weight, a high normal total blood volume was found, with a normal cell-plasma-volume ratio by hematocrit. In Case XVII, during the period of suprarenal insufficiency there was a slightly increased total blood volume according to body weight, but a decreased cell-plasma volume ratio according to hematocrit or oligocythemic hypervolemia. Determinations made eight months later during the period of improvement showed a simple normovolemia. When calculated on the basis of surface area, the relative volume values reveal practically the same degree of variation with regard to area as to weight in the entire series.

TABLE III.—BLOOD AND PLASMA VOLUME DATA IN ADDISON'S DISEASE.

TABLE III. — BLOOD AND PLASMA VOLUMES															
Case.	Date.	Sex.	Age, years.	Weight, kg.	Height, cm.	Surface area, sq. m.	Blood volume.			Plasma volume.			Hematocrit, cells, per cent.	Hemoglobin, Haldane-Palmer, per cent.	Clinical condition.
							Total, cc.	Cc for each kg.	Cc. for each sq. m.	Total, cc.	Cc for each kg.	Cc for each sq. m.			
1 (A 403755)	9-14-22	M.	53	52	165	1.59	4260	82	2660	2860	53	2530	33	64	Improved.
2 (A 401101)	M.	26	62	177	1.79	6240	100	3480	3550	57	1970	43	72	Markedly improved.
3 (A 407966)	M.	42	50	172	1.57	3920	78	2500	2740	55	1750	30	105	Improved slightly.
4 (A 59466)	5- 3-23	M.	50	58	188	1.75	4710	81	2700	2940	51	1680	39	111	Poor.
	8- 1-23	64	188	1.87	5820	91	3300	3620	57	2060	38	103	Improved.
	2-26-24	63	188	1.84	6120	97	3320	3850	61	2100	37	113	Improved markedly.
5 (A 433553)	F.	58	39	154	1.32	2900	75	2200	2120	55	1590	27	82	Poor. Died twenty days later.
6 (A 291269)	M.	53	52	170	1.71	4000	77	2340	2320	45	1360	42	112	Definite shock.
7 (A 426922)	6- 7-23	M.	31	65	173	1.79	5330	82	3000	3145	48	1750	41	119	Mild shock, poor condition.
15 (A 458373)	3-24-24	M.	24	59	170	1.65	4750	80	2880	3240	55	1950	32	106	Mild shock.
	5- 9-24	59	170	1.65	4940	83	3050	3210	54	1930	35	106	Slightly improved.
	9-15-23	M.	37	60	175	1.75	6270	104	3580	3760	63	2150	30	97	Improved.
17 (A 387986)	4- 3-24	60	175	1.75	4980	83	2850	3330	55	1900	33	110	Good.
Average	57	170	1.70	4940	93	3180	3120	54	1890	32	108	

In Case IV, three determinations of the blood and plasma volume were made within an observation period of sixteen months. The first was made during a period of marked suprarenal insufficiency in which simple normovolemia existed. The percentage hemoglobin was 111. The second determination was made four months later, when definite clinical improvement had taken place. The total blood volume had increased 1100 cc (23 per cent), the plasma volume being increased 680 cc and the cell volume 400 cc. The actual circulating hemoglobin* had increased 105 gm. (14 per cent), while the percentage hemoglobin was 103, a decrease of 7 per cent. The increase in total blood volume explains this discrepancy. This would indicate a dilution phenomenon plus hemoglobin increase, in which the percentage of hemoglobin does not reflect actual hemoglobin increase because of augmentation of total volume. The third determination, nine months later, revealed a slight increase in total blood volume, 300 cc (5 per cent), which was practically all plasma volume. Study of this case would seem to indicate that, during the period of suprarenal insufficiency the volumes were decreased, with restoration of water and hemoglobin during the recovery period. The relation of blood volume to body weight was within the normal range in all three determinations, in spite of an increase in weight of 5 kg.

TABLE IV. NORMAL VALUES IN FIFTY CASES^{1*}

	Range.	Average.
Blood water, per cent	79-83	81
Plasma water, per cent	91-93	92
Cell water, per cent	60-68	64
Blood volume, † total circulating, cc	4930-7430	6180
For each kilogram of body weight, cc	72-100†	86
For each square meter of surface area	2550-4000	3360
Plasma volume, † total circulating, cc	2960-4160	3610
For each kilogram of body weight, cc	43-59	53
For each square meter of surface area	1420-2250	2050
Cell volume in cc, total circulating	1970-3310	2550
Hematocrit cells, per cent	38-45	40

Author.	Determinations.	Hemoglobin, gm. for each 100 cc.	
		Males.	Females.
Lichtenstern	61	14.14	13.10
Williamson	900	16.60	15.55
Haldane and Smith	12	13.80	13.80
Haden§	52	15.65	15.56

* The total circulating hemoglobin is determined by the formula: 13.8 gm. (Haldane normal standard) hemoglobin times percentage hemoglobin times total blood volume.

¹*Males and females.

†According to the dye method.

‡Calculated on an erythrocyte count of 5,000,000.

§ Total volume value as high as 105 cc for each kg. have been found in three "normals." This group needs further study.

In Case XVII, oligocythemic hypervolemia was present in the first determination during the improvement period. The second determination was made sixteen months later while the patient was in relatively good clinical condition. During this interval with constant weight the total blood volume decrease was 1300 cc (20 per cent), 430 cc in plasma volume and 850 cc in cell volume. In spite of loss in cell volume, the percentage cells by hematocrit and the percentage hemoglobin had increased.

In Cases V and VI, the ratio of blood volume to body weight showed low normal values. In Case VI, with the patient recovering from shock, the hemoglobin decreased from 154 to 112 per cent within a period of six days. Unfortunately, volume determinations could not be made during the shock period. Six days later, the ratio of total blood volume to body weight was within the normal range. At this time the clinical condition was considerably improved. We believe that volume values would have been low in the acute period of suprarenal insufficiency. In Case XV, in which determinations were made within a period of eight weeks with no change in the clinical condition, practically identical volume values were found. The ratio of plasma volume to body weight was normal except in Cases IV and XVII, in which there were slightly increased values in plasma volume.

Concentration Data. The percentage blood water was increased in Cases I and V in which slight or moderate grades of anemia existed. In Cases XV and XVII, no definite anemia was present but the percentage blood water was somewhat high. In Case VI, a markedly low percentage of blood water was found. The first estimation was made while the patient was in profound shock with excessive vomiting and sweating, and with a systolic blood-pressure of 60. The hemoglobin and percentage of blood water revealed a state of marked dehydration. Six days later considerable clinical improvement had taken place. The hemoglobin had decreased 27 per cent. Definite dehydration still existed, as shown by the low percentage of cell and blood water. The percentage cell water was extremely low in the latter period (Table V).

The percentage plasma water was normal in all cases except Cases I, IV and V, in which mild hydremia was associated. In Case VI, during the shock period a low percentage of plasma water was present, which was restored to normal at the subsequent determination during the improvement period.

The percentage cell water showed considerable deviation from the accepted normal range (60 to 68 per cent). The water content of cells was abnormally high in Cases I, VII and XVII, while it was decreased in Cases III, IV and VI.

Discussion. As determined by our study, anemia is the exception rather than the rule in Addison's disease, having occurred in only slight degree in 37 per cent of the cases of this series. In only

TABLE V.—CONCENTRATION OF THE BLOOD AND PLASMA IN ADDISON'S DISEASE.

Case.	Date.	Whole blood, specific gravity.	Per cent.			Percentage, erythrocytes, hematocrit.	Percentage, hemoglobin, Palmer.	Remarks.
			Water content.	Plasma water content.	Erythrocytes water content.			
1 (A 403755)	9-14-22	1.032	88.3	94.5	77.0	33	64	
2 (A 401101)	9-18-23	85.7	94.0	72	
3 (A 407966)	9-14-22	1.047	82.5	92.5	66.0	43	105	
4 (A 59466)	11- 2-23	1.058	81.6	93.0	58.5	30	105	
	5- 3-23	1.052	82.6	92.6	67.0	39	114	
	8- 1-23	79.7	93.4	58.0	38	103	
5 (A 433553)	2-26-24	81.5	94.8	58.0	37	113	
6 (A 291269)	8-18-23	85.2	93.6	62.0	27	82	
	7-13-23	74.3	91.7	154	Patient in shock. Acute suprarenal insufficiency.
7 (A 426922)	7-19-23	71.2	93.0	41.0	42	112	
15 (A 458373)	6- 7-23	1.057	80.0	92.4	73.0	41	119	
	3-24-23	84.0	95.0	60.0	32	106	
	5- 9-24	83.5	93.4	65.0	35	106	
17 (A 389986)	9-15-23	1.050	84.7	92.4	73.7	40	97	
	4- 3-24	82.0	94.0	58.0	33	110	

one instance was marked anemia found. Since death followed within a very short period in 4 cases in which it was present, anemia may have a certain prognostic value in this disease. Repeated determinations of hemoglobin and cells reveal shifts which are explainable on the basis of volume fluctuations. The color index was 1 or less in every instance, averaging 0.9. The average hemoglobin by the Palmer method was 100 per cent in 12 cases, and by the Dare method 72 per cent for the entire series. The average cell-volume index was decreased and the average saturation index was normal in 5 cases, but Cases III and V showed indices greater than 1. The average individual cell volume was decreased. The average percentage of hemoglobin in the individual cell was increased, especially in Cases III and V.

The leukocytic formulas revealed a relatively high incidence of lymphocytes, averaging 40.5 per cent. The total number of leukocytes for each cubic millimeter of blood showed no characteristic values, varying from normal to moderate leukocytosis.

The blood and plasma volumes were determined in a series of 9 cases. The average blood volume was 93 cc for each kilogram of body weight, and 3180 cc for each square meter of surface area. Normal volumes or normovolemias existed in every case except 1, in which a slightly increased total circulating volume with a decrease cell-plasma-volume ratio, oligocythemic hypervolemia, was found, which on later examination had returned to a normal relative value.

The plasma volumes in relation to body weight and surface area revealed normal values, averaging 54 cc of plasma for each kilogram of body weight, and 1890 cc for each square meter of surface area. The ratio of cell to plasma volume was decreased in 2 instances, Cases III and V having slightly decreased total blood volumes. In the other cases, the cell-plasma-volume ratios were normal. This is interesting in view of the anemia existing in Case I, as revealed by the percentage of hemoglobin and decreased percentage of cells by hematocrit, and indicates the relatively slight anemia. It was observed in Cases III, XV and XVII, with a definitely decreased percentage of cells by the hematocrit, that the percentage of hemoglobin was fairly normal. This would indicate that the erythrocytes were small, but had an increased content of hemoglobin.

Repeated determinations of blood and plasma volume were made in 2 cases. The time between determinations varied from three months to one year, and estimations were made in the periods of acute insufficiency and recovery. Marked shifts in plasma and cell volumes were found. Although determinations have been insufficient to warrant absolute statements, it seems probable that during the period of acute insufficiency lowered volumes exist which gradually increase during the recovery cycle. The volume changes, while definite, were not sufficient to disturb the normal relation of

volume to body weight.* The fluctuations include both cell and plasma volumes, revealing dilution and contraction processes associated with variations in circulating hemoglobin. In certain cases of Addison's disease under treatment, decompensation and compensation occur in stages. The former is associated with vomiting, diarrhea, sweating, and signs of excessive loss of fluids, resulting in a dehydrated state of the blood. In 1 case during the acute stage, the percentage hemoglobin reached 154, and dropped to 112 six days later when the condition had improved. Fluctuations in plasma volume probably take place in minor degree during the course of the disease. The changes in circulating hemoglobin could be interpreted as efforts to maintain the normal cell-plasma-volume ratios. These large volume shifts suggest those observed following diuresis in edematous states. The role of epinephrin in maintaining capillary permeability might be the factor explaining the volume changes.

The concentration values of the blood were definitely high in Case VI. This patient was extremely intolerant to epinephrin. With the administration of epinephrin, the systolic pressure dropped to a shock level. There was marked sweating, with vomiting and diarrhea, and during this period the hemoglobin was high. Following treatment to restore the fluids, such as application of heat, gradual improvement occurred. Six days later, repeated examinations revealed considerable improvement in the percentage of water in the blood and the hemoglobin had decreased markedly. This condition is extremely interesting, and possibly represents a sudden alteration in capillary permeability associated with the administration of epinephrin. Rowntree observed, in one instance, during the periods of acute epinephrin insufficiency, that small doses of epinephrin seemed to have no, or perhaps a deleterious effect, but when the full Muirhead treatment was used, there was a spectacular or marked beneficial response.

Summary. Of 17 cases of Addison's disease observed at the Mayo Clinic, definite anemia was present in only 1 (6 per cent). A mild or questionable anemia was found in 4 cases (23 per cent). In 3 of 5 cases the cell-volume index was decreased, and in three the saturation index was increased, indicating small erythrocytes with high hemoglobin content. A relatively high lymphocytosis was present in the majority of cases.

According to the dye method, normal circulating blood and plasma volumes, or simple normovolemias were found in all but 1 case. Decreased percentages of water and of blood and plasma were observed in 1 case during the period of acute suprarenal insufficiency. Anemia, when associated with Addison's disease, is apparently not due to a dilution, or an increase in total blood volume, since large blood volumes did not exist in the presence of anemia.

* Repeated blood and plasma-volume determinations by the dye method in normals have had a remarkable constant relation to body weight.

Anemia was not masked by contraction of volume, since normovolemia existed in all cases in which hemoglobin values were normal. Repeated volume determinations in 3 cases revealed in 2 marked fluctuation in cell and plasma volumes. The volume fluctuation masked only in a minor degree the percentage hemoglobin changes, since the normal cell-plasma-volume ratios were closely maintained.

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THE LEUKOCYTIC PICTURE IN CATARRHAL JAUNDICE (CHOLANGITIS).

BY ETHEL THEWLIS,

AND

WILLIAM S. MIDDLETON, M.D.,

MADISON, WIS.

(From the Department of Clinical Medicine, University of Wisconsin.)

THE wide divergence of opinion concerning the actual clinical picture and the underlying pathology of acute catarrhal cholangitis

doubtless explains the lack of unanimity with regard to its blood-picture. The extension of a catarrhal inflammation from the duodenum into the larger bile passages or an obstruction of these ducts by plugs of mucus are the commonly accepted explanations for this condition. However, the existence of an involvement of the finer bile radicals seems highly probable in view of the clinical course of certain cases of catarrhal jaundice, and, too, this process has been definitely proven in other cases coming to necropsy.¹

Until the comprehensive studies of Jones and Minot,² no serious effort to establish a clinical entity in relation to acute catarrhal jaundice had been attempted. The characteristic clinical picture in the type of jaundice under discussion in this presentation commonly succeeds an acute upper respiratory infection by from five to fourteen days. Prodromal symptoms of lassitude, anorexia and headache are experienced for several days before the febrile manifestations of the disorder. The onset of the febrile reaction is accompanied, as a rule, by rigor, nausea and vomiting with or without upper abdominal distress or acute epigastric pain. Constipation with the classical clay-colored stool is the rule. At times diarrhea may attend the early stages of this affection. Extreme discomfort, restlessness, in part from the severe headache, and general malaise are remarked in the early febrile period. The temperature may range from 100° to 104° F. for three to five days before the appearance of skin pigmentation. Itching about the eyes may precede the visible jaundice which is first remarked in the sclerae and the soft palate. The general cutaneous surface quickly becomes tinged to a greater or less extent and all secretions, such as urine, smegma, and so forth, are likewise stained with bile pigments. Itching may become intense. Bradycardia is practically a constant finding. An enlarged somewhat sensitive liver may be determined very early in the febrile period. A majority of these cases show moderate splenic enlargement.³

The uncomplicated case of acute catarrhal jaundice responds promptly to simple dietetic and medical treatment. In mild cases the temperature falls to normal within three or four days; the subjective symptoms of gastric distress, nausea and vomiting usually subside with the fever; bile reappears in the stool in from six to ten days and the icterus simultaneously begins to fade. The complete disappearance of bile pigments from the urine usually antedates the loss of skin pigmentation by days or even weeks. Physical and mental depression are experienced for a considerable but variable period after the subsidence of acute symptoms.

Since the leukocytic reaction forms an important element in the composite picture of any infectious disease, it is interesting to examine the standard authorities with reference to this factor in catarrhal jaundice. No especial mention of this matter is found in the systems of medicine with the exception of Tice,⁴ who states that

there is seldom an increase in the white blood corpuscles, though they may go up to 10,000. Von Limbeck⁶ remarks no leukocytosis in simple, uncomplicated catarrhal jaundice. Cabot⁶ states that a constant leukocytosis excludes uncomplicated catarrhal jaundice and points to malignancy or inflammation. Eighteen isolated numerical white cell counts are given, ranging from 4000 to 10,500. In this group ten counts are below 7500. Da Costa⁷ quotes figures for the white cell count of catarrhal jaundice varying from 3600 to 26,000 with an average of 9361 in 40 cases. His cases without reference to the stage of the disease or the nature of the case are grouped thus:

Leucocytes.	Number of cases.
20,000 to 30,000	4
15,000 to 20,000	0
10,000 to 15,000	4
5,000 to 10,000	29
Below 5000	3

Emerson⁸ lists 27 cases, in 20 of which the leukocytes numbered 10,000 or less; 3, 10,200 to 10,500 and 4 between 14,200 and 19,500. He remarked a rapid fall to normal after admission to hospital and quotes Bezançon and Labbé to the effect that a leukopenia follows in some cases.

A paucity of data on the numerical white cell count and an absence of a differential picture for catarrhal jaundice, therefore, existed until the above cited work of Jones and Minot.² The results of their extensive observations in this direction may be summarized as follows:

The white cell count is early increased, but rarely exceeds 10,000. This increase lasts but a few days and is succeeded by a leukopenia. The lowest recorded count was 2000 and occurred in a very severe case. The leukocytes commonly fall below 4000 and the lowest level occurs a few days after the beginning subsidence of the jaundice. Return to normal is gradual, occupying a period varying from days to weeks. Leukocytosis is remarked only in complications.

The differential picture shows an early normal distribution or slight increase in the polymorphonuclear neutrophils succeeded by a sharp drop in these cells (lowest 31 per cent in 5200) coincident with the fall in total leukocytes. There is an accompanying rise (relative and absolute) in lymphocytes and large mononuclears. With certain variations, these types assume their highest level at the height of the jaundice. Fifty to 60 per cent were high points for the lymphocytes, while the large mononuclears frequently reach 10 per cent. Eosinophiles and basophiles are usually within normal range. The eosinophiles, however, occasionally exceed 5 per cent of the total white cells. Especial attention is directed to the immaturity of the lymphocytes and the neutrophils and to the appearance of vacuolization in the several forms of white cells.

LEUKOCYTIC PICTURE IN CATARRHAL JAUNDICE.—(Continued.)

AFTER ONSET OF JAUNDICE.

Case No.	White blood cells.	Neutrophils.		Eosinophils.		Basophils.		Lymphocytes.				Lymphoblasts.		Large mononuclears.		Transitionals.	
		Per cent.	No.	Per cent.	No.	Per cent.	No.	Small.		Large.		Per cent.	No.	Per cent.	No.	Per cent.	No.
								Per cent.	No.	Per cent.	No.						
1*	14,000							DAY OF ONSET.									
7	8,000							Tot.	30%	1980	4.0	264
12	6,600	61.0	4026	3.0	198	2.0	132	Tot.	27%	1836	5.0	340
20†	17,200							Tot.	28.5	798	8.0	224	4.0	112
23	6,800	66.0	4488	2.0	136	Tot.	28.5	1425	0.5	25	11.5	575
26	2,800	57.5	1610	2.0	56	Tot.	36%	2664	3.5	259	1.5	111
27	6,200							Tot.	23.4	2340	8.0	800		
28	5,000	58.0	2900	0.5	25	1.0	50	Tot.	35.6	1139	12.4	397	0.2	6	0.4	13	
29	7,400	57.5	4255	0.5	37	1.0	74	Tot.	20.0	480	5.2	125	0.8	19	9.8	235	0.2
33	10,000	67.4	6740	0.4	40	0.2	20	Tot.	1139	12.4	397	0.2	6	0.4	13		
35	3,200	50.2	1606	1.0	32	0.2	6	Tot.	20.0	480	5.2	125	0.8	19	9.8	235	0.2
36	2,400	60.0	1440	3.2	77	0.8	19	Tot.	20.0	480	5.2	125	0.8	19	9.8	235	0.2
37	4,800																
43	4,400																
Average	7,570																
ONE DAY.																	
2	4,600																
3	6,800																
4	5,200																
10	11,000																
14	5,000																
19	5,200	64.0	3328	3.0	156	Tot.	29%	1508	1.0	52	3.0	156
22	8,400																
25	4,800																
26	4,600	62.0	2852	1.0	46	0.5	23	Tot.	26.5	1219	8.0	368	2.0	92
27	2,800	29.5	826	0.5	14	0.5	14	Tot.	58%	1624	8.5	238	2.0	56
36	5,800	54.2	3144	1.8	104	1.2	70	Tot.	21.0	1218	5.6	325	0.4	23	15.8	896	
38	4,000																
41	7,200	66.6	4795	0.8	58	Tot.	16.2	1166	16.0	1152	0.4	29			
43	4,200	50.2	2108	2.4	101	0.8	34	Tot.	38.2	1604	8.0	336	0.2	84	
Average	5,685																
TWO DAYS.																	
7	8,600																
9	5,400																
11	7,000																
16	8,600	47.0	4042	2.0	172	Tot.	45%	3870	3.5	301	2.5	215
17	7,000	58.0	4176	6.0	432	Tot.	30%	2160	6.0	432
18	8,200																
25	4,200	53.0	2226	4.0	168	Tot.	38%	1596	4.0	168
27	5,200																
35	4,400	42.8	1883	3.4	150	0.6	26	Tot.	34.4	1514	16.8	739	2.0	88	
36	2,400	60.0	1440	3.2	77	0.8	19	Tot.	20.0	480	5.2	125	0.8	19	9.8	235	0.2
37	2,800	45.6	1277	1.8	50	0.4	11	Tot.	37.6	1053	12.8	358	0.8	22	1.0	28	
Average	5,800																
THREE DAYS.																	
36	6,000	63.8	3828	1.4	84	0.2	12	Tot.	15.8	948	3.4	204	1.4	84	14.0	840	
38	4,600	45.6	2098	1.6	74	0.4	18	Tot.	43.0	1978	8.8	405	0.6	28			
44	1,200	46.6	559	1.0	12	0.2	2	Tot.	32.8	394	16.8	202	1.0	12	1.6	19	
FOUR DAYS.																	
36	4,800	48.0	2304	3.0	144	0.5	24	Tot.	29.0	1392	6.0	288	13.0	624	
42	8,600																
37	5,200	51.8	2694	1.8	94	0.8	42	Tot.	31.0	1612	10.6	551	0.8	42	3.2	166	
FIVE DAYS.																	
36	3,600	53.0	1908	2.0	72	0.8	29	Tot.	26.6	958	7.6	274	0.4	14	9.6	346	
37	6,400	45.4	2906	2.6	166	0.4	26	Tot.	37.8	2419	11.4	730	1.0	64	1.2	77	0.2
SIX DAYS.																	
15	6,000																
36	2,800	55.2	1546	3.6	101	1.0	28	Tot.	23.2	650	6.8	190	0.2	6	9.8	274	0.2
42	4,400	44.0	1936	3.8	167	0.4	18	Tot.	42.8	1883	7.0	308	1.4	62	0.6
SEVEN DAYS.																	
36	4,400	40.8	1795	4.0	176	0.8	35	Tot.	42.4	1848	6.4	282	0.2	9	5.8	255	
37	4,000	53.0	2120	2.2	88	1.2	48	Tot.	30.0	1200	11.8	472	0.6	24	1.0	40	0.2
EIGHT DAYS.																	
16	8,800	59.0	5192	1.0	88	1.0	88	Tot.	36%	3168	1.5	132	1.5	132
36	3,200	47.6	1523	4.0	128	0.4	13	Tot.	30.0	960	6.4	205	0.4	13	10.8	346	0.4
44	3,800	45.8	1740	1.0	38	0.8	30	Tot.	41.2	1566	8.0	304	1.2	46	2.0	76	
NINE DAYS.																	
30	9,000																
36	4,400	42.8	1883	4.2	185	0.8	35	Tot.	32.2	1417	9.8	431	2.0	9	9.6	422	0.4
44	3,200	58.0	1856	1.8	58	Tot.	31.0	992	6.8	218	0.4	13	1.8	58	0.2

* Case 1. Diarrhea for two days. † Case 20. Vomiting copiously for two days.
 Excluding Cases 1 and 20, average total leukocytic count for the remaining 12 cases on the day of onset of jaundice was 5633.

In Chart I the numerical leukocytic counts have been plotted to demonstrate better the distribution of these figures. It immediately becomes apparent that only a small minority of the counts

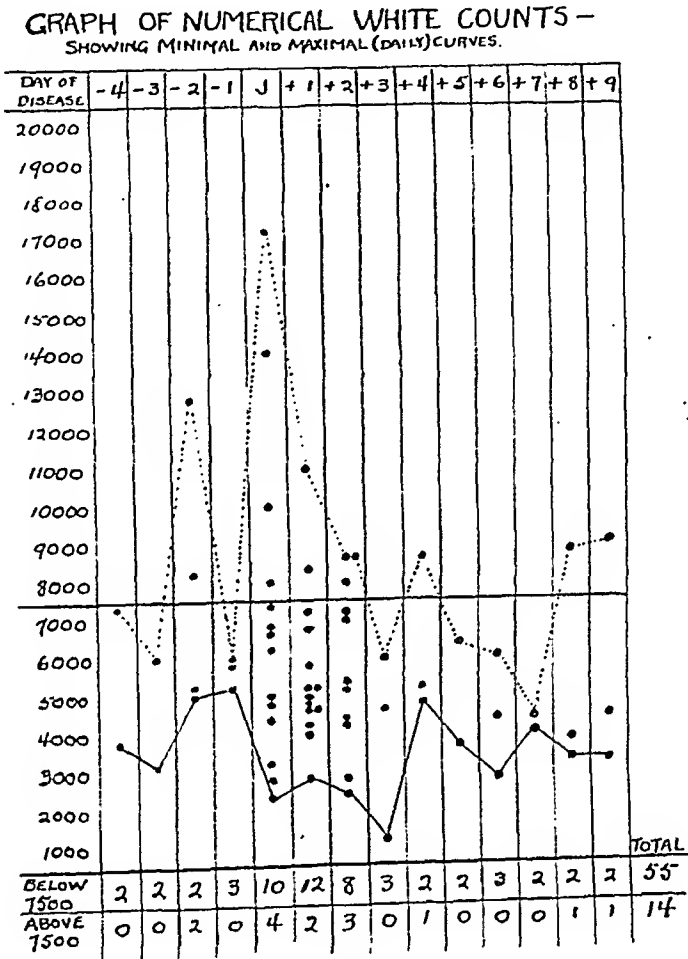


CHART I.

(14 of 69—20.2 per cent) exceed the average normal level. A further analysis of the total leukocytic counts in the 38 cases under study shows at the highest recorded level for each individual case the following:

Leukocytes.	Cases.
Over 15,000	1
10,000 to 15,000	4
7,500 to 10,000	9
5,000 to 7,500	17
2,500 to 5,000	7

The tendency to leukopenia is quite definite and, contrary to the contention of Jones and Minot, is an early finding in catarrhal jaundice. Indeed, a majority of the studied cases showed a definite leukopenia not only at the very onset of the manifest jaundice but

several days before its appearance. With the development of jaundice the reduction of the white corpuscles becomes pronounced. The lowest count, 1200, (Case 44) was recorded three days after the onset of jaundice. The period of leukocytic depression is variable and apparently in a measure dependent upon the severity of the underlying condition. A return to the normal leukocytic level occupies from ten to fourteen days in the average case, and is commonly preceded by a postfebrile reactive leukocytosis (Chart II).

The differential leukocytic picture of catarrhal jaundice offers certain difficulties of translation unless the absolute counts be given due consideration. Confusion is bound to result from discussion of the relative or percentage changes in the various cells. A characteristic case has been charted with an analysis of the component cells (Chart II).

Beginning with the second day after the onset of jaundice this case has been followed for fifteen days. A depression of polymorphonuclear neutrophiles (normal, 3780) is immediately noted, which continues for ten days. This fall in the neutrophilic count is relatively constant (see Table), notable examples being Case 27 on the first day after the onset of the jaundice and Case 44, three days after the onset. In the former the neutrophiles numbered only 826 (29.5 per cent of 2800), whereas a figure of 559 (46.6 per cent of 1200) was established for these cells in the latter. High relative lymphocytic counts may lead to an erroneous conception of a replacement of the neutrophiles by these cells. However, it becomes apparent that this discrepancy results not from an actual increase in the lymphocytes (normal, 2475) but from a disproportionate reduction in the neutrophiles (Table and Chart II). Indeed an absolute lymphocytosis is most unusual in spite of occasional relative changes as high as 58 per cent with the polymorphonuclear neutrophiles at 29.5 per cent in a total white cell count of 2800 (Case 27, one day after the onset of jaundice). In Chart II the lymphocytes resume their normal absolute level simultaneously with the neutrophiles in spite of relative preponderance over the latter at several points in the earlier days of the disease. Unusual young forms of lymphocytes and the common appearance of lymphoblasts bespeak a definite stimulation of the lymphoid centers. Furthermore, there is, commonly, an absolute increase in the large mononuclear cells (normal, 120), the highest level being recorded in Case 36 on the first day after the onset of the jaundice (15.8 per cent of 5800 — 896). The transitional cells are practically always below the normal absolute level (555). The eosinophiles (normal, 240) and basophiles (normal, 60) partake of the general decrease in polymorphonuclear forms with certain well-defined exceptions in the case of the first named. In Case 6 on the second day prior to jaundice (5.8 per cent of 12,800 — 742) and in Case 17 two days after the onset of jaundice (6 per cent of

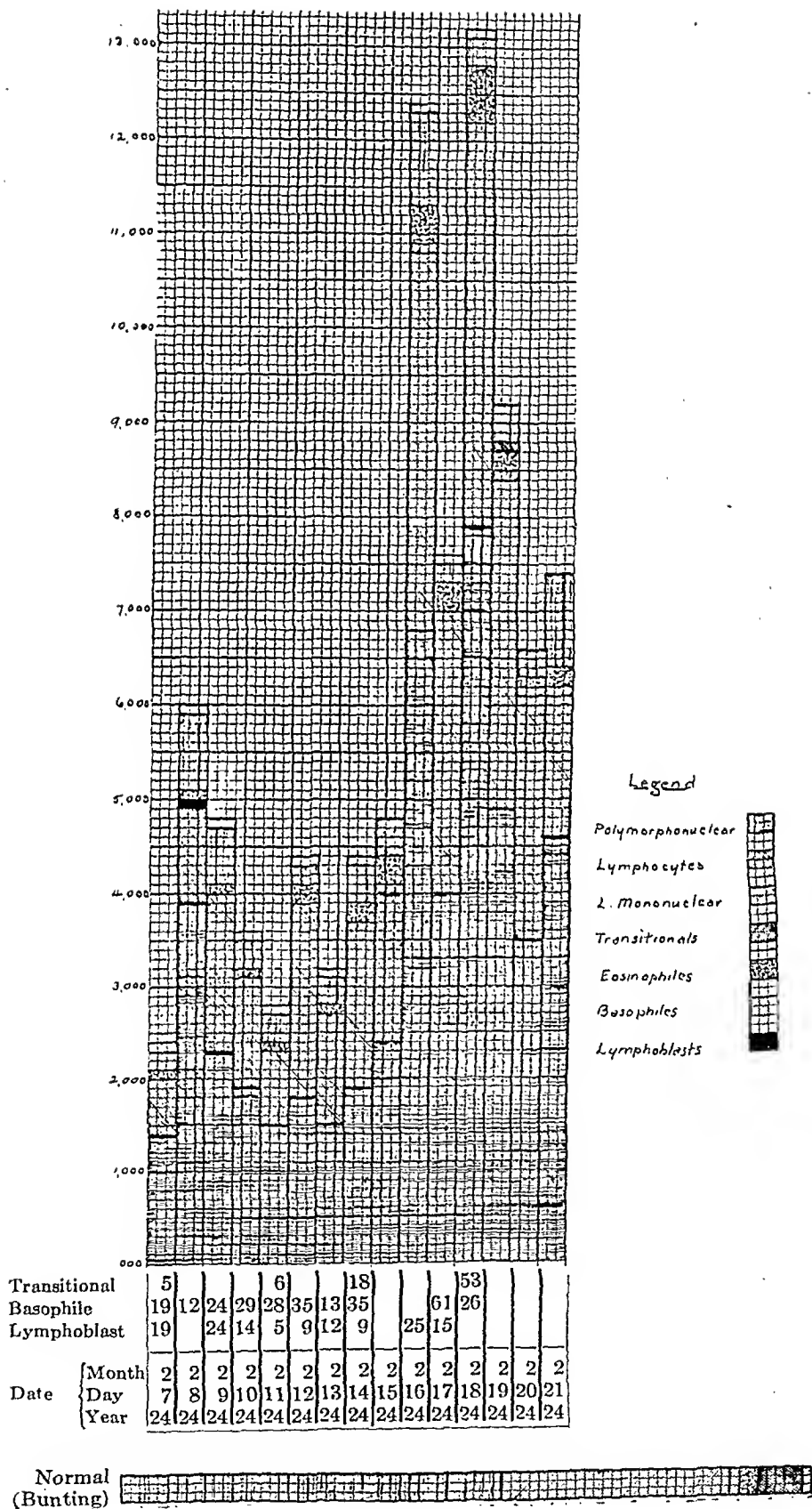


CHART II

7200 — 432), increases in both the relative and absolute figures for the eosinophiles were determined.

Discussion. The leukocytic picture in a series of 38 cases of catarrhal cholangitis is presented. Notable among the findings in this relation are the leukopenia, the absolute decrease in all of the component white blood corpuscles except the large mononuclear cells and the appearance of unusual lymphocytic forms, especially the lymphoblast. Preliminary studies indicate that the fall in polymorphonuclear neutrophiles results from inhibition rather than paralysis of the leukogenetic function. The suggestion of a continued hemoclastic shock in explanation of the observed leukopenia in the presence of a known hepatic lesion has not been fruitful.

Summary. 1. Leukopenia is an almost constant blood finding in uncomplicated catarrhal cholangitis. In a certain percentage of cases it may precede the appearance of the jaundice. In cases followed long enough a definite postfebrile, reactive leukocytosis is remarked.

2. The polymorphonuclear neutrophiles suffer more than any other white-blood element in the primary depression.

3. This disproportionate decrease of the neutrophiles leads to a relative lymphocytosis, but the actual number of these elements is decreased as a rule.*

4. The large mononuclear cells alone appear to be constantly increased in catarrhal jaundice.

5. In moderate cases a return to the normal numerical and differential counts occurs within two weeks.

From a practical standpoint these data should serve as important diagnostic criteria. Prognosis in catarrhal jaundice may be guided by the degree of the leukopenia and the trend of the leukocytic curve. As has been intimated, the degree of leukocytic depression is frequently in direct ratio to the severity of the underlying condition. Furthermore, the lowering of resistance incident to a decrease in the leukocytes in catarrhal cholangitis must impress the practitioner with the necessity for the protection of such individuals from exposure to infectious disease, until a normal leukocytic level has been reestablished.

* Jones and Minot's conclusions of an early primary leukocytosis, transient in nature and minor in degree, and of an almost constant absolute lymphocytosis "in spite of the leukopenia" which supervenes, are in disagreement with these findings. In justice to these workers it should be stated that a critical review of their data shows a leukopenia in a majority of cases from the onset and, too, the instances of absolute lymphocytosis are the exception rather than the rule. Such instances apparently occur more commonly than have been remarked in the present study but far less frequently than the conclusions of Jones and Minot would infer. In a word a definite but inconstant tendency in this direction is noted throughout the course of a small minority of their cases, and more especially in the presence of a leukocytosis.

If these two points of difference be reconciled, it will become apparent that the present studies closely corroborate the work of Jones and Minot.

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THE INFLUENCE OF EMOTIONAL REACTIONS ON BASAL METABOLISM.*

BY LLOYD H. ZIEGLER, A.M., M.D.,

PHIPPS PSYCHIATRIC CLINIC, JOHNS HOPKINS HOSPITAL,

AND

B. S. LEVINE, PH.D.,

DIRECTOR OF CLINICAL LABORATORY, U. S. VETERANS HOSPITAL NO. 37, WAUKESHA,
WISCONSIN.

THIS study was prompted by the observation that basal metabolism readings of psychoneurotic individuals without goiter, no matter how careful the technic, are sometimes high.¹ In an attempt to learn something of this problem methods were used to determine the effect of emotions on basal metabolism. Patients were selected who were known to have aspects to their past history which were emotion producing. None of them had a goiter.

A patient was placed on the bed after the usual preliminary preparation for a basal metabolic rate which was determined by the Tissot-Haldane method. Other points in the technic were carried out as described by one of us.² Three basal metabolic tests were made which were identical except that during the second the patient was asked to keep quiet as before, but to think about something (the thing was suggested to the patient) which from his history would seem to induce emotions. The patient was under careful observation all of the time during the second test, for objective signs of emotional responses. Notes were taken. Before each test the patient was urged to be as quiet as possible. After all of the tests had been made the patient was interviewed to ascertain what his subjective feelings had been. It will be observed that by this procedure the test in which the patient was expected

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to have emotional responses was sandwiched, so to speak, between two control tests.

Two case histories, at this point, with the actual data of the tests, will serve to show more exactly the procedure of the study.

Case Reports. CASE I.—C. B. F., aged thirty-four years, single, farmer, college graduate, complained of being torn up by the slightest excitement; he said his heart would beat rapidly and he would become short of breath, and had difficulty in talking at these times. He comes of a family in which a paternal uncle developed mental changes after an injury to the head; another paternal uncle lived a hermit's life after domestic trouble; a maternal uncle was insane; a maternal aunt was nervous; and one sister of the patient developed a kind of paralysis of the legs and was in bed weeks following a minor excitement, from which she recovered. The patient had always been reserved and retiring and was occasionally depressed. His early life was uneventful from the standpoint of disease or circumstance until he had reached high school when he was troubled with his eyes, was restless, and had a slight speech defect. He slept poorly and said he always had a feeling that something was going to happen. He was fitted with glasses and the symptoms were less bothersome. In college the speech defect returned but he struggled with his "weakness" by taking a course in public speaking. He had a good occupational record.

In 1918, the patient was drafted into the United States army and soon became markedly upset by the restrictions and discipline of the army. On the way overseas he met with some unpleasant experiences in the influenza epidemic, and contracted the disease himself, from which he recovered slowly because of insomnia, weakness and rapid heart. Thereafter, he had some difficulty in speaking to some officers who were rather rough to him, and a marked degree of "self consciousness" with a violent distaste for army life developed, which upon his return home caused him to seclude himself assiduously.

The only positive physical findings on admission to the hospital were some mild dental caries, blood-pressure 102-70, and bilateral pes planus.

From the behavioristic standpoint he showed a tendency to be alone and become agitated and markedly restless. Whenever army life, and his own army experience in particular, was mentioned, he showed much disgust.

The data of the test are given in Protocol I.

PROTOCOL I. C. B. F.—Anxiety Hysteria. September 5, 1922, 9.30 to 10.30 A.M.

Stimulus Remarks for Test B. Remain quiet as before and think over in the next ten minutes your army experiences, especially the more disagreeable ones.

Objective Observations during Test B:

- 10.00½ Test began (stopcock opened). (Began to detail stimulus remarks).
- 10.03 Face flushed; quiet; eyes closed.
- 10.04 Breathing becomes heavier; quiet.
- 10.04½ Takes occasional larger breath; quiet.
- 10.05 Breathing irregular in rhythm; otherwise quiet.
- 10.07 Slight fine tremor in respiratory movements as if large movements would break up into many smaller ones.
- 10.08½ Whole upper half of body shows definite fine tremors; face slightly flushed.
- 10.09 Fine tremors of upper half of body continue. Presents slight facial contortions or grimaces; eyes shut; face flushed.
- 10.10 Fine tremors, more marked in upper half of body; smiles; face continues flushed.
- 10.10½ Stopcock closed.

Subjective Reactions during Test B. Felt confined by the local discomfort of having nose pinched. Did not think he would get worked up like he did. Was disgusted and somewhat angered to think he would react as much as he did. Said he had a real emotional disturbance in which he could feel his heart beat more rapidly, with a dull sensation in the region of the heart.

Metabolic Readings:

B. M. R. (first
control) A
+9.62

B. M. R. (emo-
tional response) B.
+28.9

B. M. R. (second
control) C
+13.9

CASE II.—S. J., aged thirty-two years, married, bookkeeper, complained of headaches with pain in back of head on stooping, restlessness, insomnia, fear of insanity, and with an impulse to scream when in public places. He comes of a family free from nervous and mental diseases. Aside from being a quiet and uncommunicative youth, there was nothing unusual in his early history. He was an average student in school, having reached the seventh grade when he quit to go to work. He worked quite regularly until enlisting in 1917. Soon thereafter he was detailed to be a male nurse in the Medical Department in a camp in the United States. Once was ill after being struck by an automobile, after which his headaches and dizziness began. Soon thereafter, while on night duty, he was accused of being asleep, was severely reprimanded, reduced in rank, and placed in the guardhouse for thirty days. Certain other grave punishments were held before him as possibilities. He was very much worried by the affair and felt differently thereafter.

Physical findings revealed a few dry rales over the right apex

posteriorly, clubbing of all fingers and toes, fine tremors of extended fingers, bilateral hyperopia, and dental caries and gingivitis.

He showed on admission to the hospital considerable anxiety and restlessness, especially when talking over the painful incidents of his army life, and on a few occasions tears came into his eyes. He was somewhat suspicious, but had no definite delusions, ideas of influence, ideas of reference, or hallucinations. Protocol II gives the data of the laboratory tests and observations.

PROTOCOL II. S. J. Anxiety Neurosis. September 21, 1922.
9.00 to 10.00 A. M.

Stimulus Remarks for Test B. Be quiet as before and in the next ten minutes think over your army experiences, especially the unpleasant ones.

9.39 Stopcock opened. (Began to detail stimulus remarks.)

9.40 Quiet; normal.

9.41 Face pinker.

9.42 Face pink. Breathing increased in amplitude and rate. Bats eyes frequently.

9.43 Breathing heavily.

9.44 Heavy breathing.

9.45 Slight tremor of upper extremities; tears appear at eyes and run down over cheek; face red; apparent suppressed crying.

9.46 Breathing irregular.

Subjective Reactions. Patient stated that the remarks made him markedly blue and depressed for the time being. Said his emotions were intense and were most intense about the middle of the test.

Metabolic Readings:

B. M. R. (first
control) A
-2.8

B. M. R. (emo-
tional response) B
+40.0

B. M. R. (second
control) C
+.8

It has been known that emotions affect the metabolism readings and are to be avoided, where possible, in arriving at conclusions for diagnostic purposes. In this study the variations in heat production induced by thinking of certain things, usually of an undesirable nature, were interesting for several reasons. Table I gives the data for 14 psychiatric patients with various diagnoses. One patient was given the test twice.

To the casual observer the majority of these patients would have been considered during the test as lying still on the bed. It was recorded in the case of 4 that there was restlessness, which was small in 3 cases. The most constant objective reactions observed were small changes in amplitude and rate of respiration, very fine tremors, and changes in the color of the face from normal to a flushed face, as in blushing, with irregular variations throughout the second test.

TABLE I.

Diagnosis.	Metabolism.			Feelings during test B, subjective.	Detailed objective observation during test B.	Summary of objective observations.
	A.	B.	C.			
S. J. (anxiety neurosis)	-2.8	+40.0	+0.8	Depressed	Flushing of face; change in respiratory rate and amplitude; few tremors in upper part of body; tears in eyes.	Very slight reaction.
C. B. F. (anxiety hysteria)	+9.6	+28.9	+13.9	Disgust; anger	Flushed face; change in respiratory rate and amplitude; fine tremors in upper part of body	Very slight reaction.
J. H. (anxiety hysteria)	+7.0	-8.0	+3.5	Slightly depressed	Flushed face, change in breathing amplitude and rate; breathing with lungs full; occasional small twitch	Nothing unusual.
J. H. (retest with new stimulus remarks)	-1.3	-5.6	-3.5	"Peeved;" more feeling than on previous test.	Same as above; no tremors; alert	Nothing unusual.
C. E. R.* (anxiety hysteria)	+12.4	+14.0	+4.3	Excited feeling	Coughed few times, restless, occasionally moving arm or leg or head about slightly	Slightly restless.
P. O. C. (anxiety hysteria)	+7.8	+23.0	+4.6	No emotional reactions	Flushed face; possibly some change in breathing amplitude	Nothing unusual.
B. L.† (anxiety hysteria)	-2.5	+17.2	+14.9	Tense and excited	Slight tremors of neck and shoulders; face not changed	Very slight reaction.
S. E. (hysteria)	+11.4	+31.9	+13.2	No emotions; local nasal discomfort	Restless, moves legs, arms, and head about; small tremors about face and neck; breathes irregularly	Slightly restless.
S. H.‡ (hysteria)	+6.5	+21.0	+13.1	Excited	Face pink to red; tremors of face and neck; tremors increased to end of test; breathing irregular	Restless.
S. R. (hysteria)	+5.8	+13.9	+12.2	Slightly depressed	Changes in color of face; possibly amplitude of breathing slightly increased	Nothing unusual.
Y. H.§ (neurasthenic type)	+0.2	+8.6	-5.6	None	Face pink; slightest restlessness for short time	Nothing unusual.
S. W. (neurasthenic type)	-1.1	+22.0	+8.7	None	Face pink; probable slight increase in amplitude of respiration	Nothing unusual.
S. B. F.** (neurasthenic type)	+8.8	+24.6	+9.2	Excitement in which heart felt accelerated and breathing came harder	Face pinker at times	Nothing unusual.
R. C. J. (constitutional psychopathy with depressive and anxiety features)	+3.0	+15.2	+8.6	Slightly excited	Slight tremor of upper part of body; shallow, frequent respirations; some squirming	Very slight reaction.
L. N. (constitutional psychopathy with schizophrenic features)	+20.5	-1.3	+50.9	Revulsive feelings	Grimaeces of face; respiration deep and slow; eyes opened and closed; face pink; tried to speak a few words	Restless.

* Felt more fatigued than usual at the end of the day on which test was made.

† The test initiated an excitement which he could feel all day.

‡ Reacted by marked tics and muscle spasms for twelve hours after the test.

§ More study of Y. H. revealed fact that stimulus remarks used were not "his chief preoccupation."

** Said he was always so fatigued that emotions were short-lived.

NOTE.—There seems to be little correlation between the change in metabolism and the objective manifestations of emotions.

Subjectively, the reactions varied; 3 said they felt depressed; 1 reacted by a combination of anger and disgust; 1 reacted by being "peevish" and 1 by revulsive feelings; 5 said they were more or less excited; 4 had no feelings whatsoever. On J. H. two tests were performed with different stimulus remarks and the emotional responses differed with a reduction in the metabolic rate in either test.

Chart I presents in graphic form the metabolism readings for the group and shows rather strikingly the tendency for the rates to increase in the majority of cases. There are indications, however, that emotions affect metabolism in opposite ways and this suggests the possibility of two distinct types of people.

The preliminary nature of this study is evident from the few cases studied but nevertheless Table I presents some interesting facts corroborated by clinical observation. One of the most striking facts is the failure of some patients to recognize any emotion though readings clearly indicated a rise of metabolism. This offers one hopeful explanation for the insidious way in which neurasthenic individuals may dissipate their energy. Another important fact is the change in metabolism in a few cases without objective evidences except small vasomotor phenomena, very fine tremors, and slight changes in respiratory rate and amplitude. These give clues for the detailed study of the elusive emotional states. Two patients, P. O. C. and S. W., had no subjective feelings and very slight objective behavior changes. Except for the change in metabolism, practically nothing would have been known of the de-energizing tendency of the stimulus remarks about which these patients were preoccupied almost continually. By comparative studies³ it was shown that some of the patients' emotional reactions, in terms of energy expended, were equivalent to that of an ordinary hospital ward patient, or from one-third to one-half of the energy necessary for the same patient to do the work of a merchant tailor.

No characteristics peculiar to the different neurotic types was ascertainable with such a small number. The study bears out what most clinicians have long observed, viz., that the mere fact of a patient lying quietly in bed, is no assurance of a state of rest. The pharmacodynamic importance of certain ideas and imaginations, obsessive thoughts, painful reminiscences and complex material, is at once apparent. It must be evident that unless something is known about the life problems of a patient and their effect on him, mistakes of diagnosis may easily follow from too much dependence on basal metabolic determinations. This is all the more true in a region such as the Great Lakes district where a rather high per cent of all people have goiter. The energy governing mechanism of subtle emotional reactions should stimulate study of such a disease entity as exophthalmic goiter, the etiology of which seems definitely disputed, to determine what components of it may be

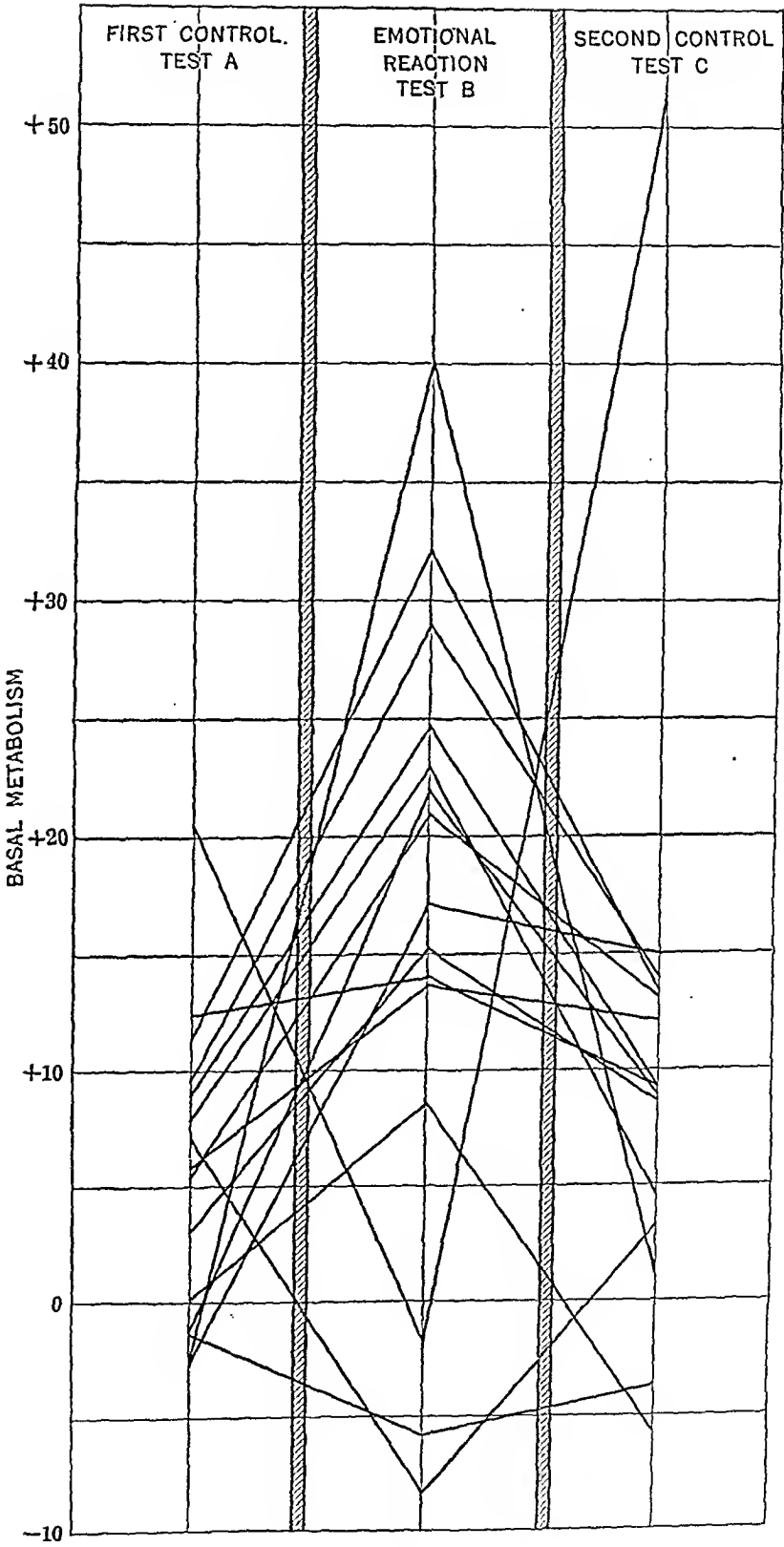


CHART I.

actually due to the secretion of the thyroid and what may be due to a lowered threshold for emotional reactivity.

Summary. 1. Basal metabolism above normal in some psychoneurotic individuals without goiter prompted an inquiry into the mechanism of the deviations.

2. Psychoneurotics without goiter usually respond when thinking about an emotion-producing aspect of their past history, by an increased metabolic rate.

3. Most frequent objective responses to emotion-producing stimuli were small changes in color of skin, slight change in rate and amplitude of respiration, and very fine tremors.

4. Some patients who showed increase in metabolism and practically no objective reactions, were not aware of any emotions whatsoever.

5. The pharmacodynamic influence of unpleasant memories, ideas, and worries is a subject worthy of much investigation in order to understand the phenomena of disease and discomfort, and the conservation of human energy.

6. Lying apparently still in bed is not to be taken as a criterion of rest.

7. Exophthalmic goiter with disputed etiology should be studied to see what components are due to secretion of thyroid and what may be due to lowered threshold of emotional reactivity.*

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THE ELECTROCARDIOGRAM IN UREMIA AND SEVERE CHRONIC NEPHRITIS WITH NITROGEN RETENTION.

BY J. EDWIN WOOD JR, M.D.,

AND

PAUL D. WHITE, M.D.,

MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS.

A PREVIOUS publication¹ from the Massachusetts General Hospital has called attention to the fact that disturbances of cardiac mechanism are not uncommon in uremia. We have made a more detailed study of 38 cases of uremia and severe chronic nephritis with nitrogen retention to determine whether abnormal electrocardiographic changes may be ascribed to the toxic effect of the products of uremia upon the heart muscle. The effects of digitalis, myxedema, myocardial degeneration and disease of the conduction system have been excluded so far as possible.

There is little in the literature on this subject. Lewis² has noted that many poisons may act upon the end-deflection of the electrocardiogram but that the initial phases are less liable to change of form and direction. Cohn³ has described the effects of digitalis and atropin on the *T* wave. He also mentions the fact that muscarin will invert the *T* wave. Kraus and Nicolai⁴ say that in poisoning there may be first an increase, then a decrease in the *T* wave. They also note that decrease or disappearance of the *T* wave may occur in loss of blood and in chloroform narcosis.

All of these writers refer to exogenous poisons. Among the toxins of endogenous origin which affect the heart that of thyroid disease is perhaps one of the commonest. The toxin of this disease however causes only changes of heart-rate at first and not until secondary heart muscle changes set in is the form or direction of the complexes

of the electrocardiogram notably changed. The toxins of various diseases will cause changes in rate but probably none of these with the exception of the toxin in diphtheria produces changes in the form of the electrocardiogram. We believe that a toxemia occurs in uremia which affects the heart muscle in certain instances so that a change in either the form or direction of the electrocardiographic complexes may occur. Heitz⁵ recalls that in 24 of his 25 cases of pulsus alternans there was uremia. Chaher and Centaminin also found uremia in 7 of their 10 cases of pulsus alternans. Both hypertension and uremic poisoning were probably factors in these cases.

Thirty-eight cases of uremia and severe chronic nephritis with increased blood nitrogen have been studied at the Massachusetts General Hospital with reference to the electrocardiogram. All showed a non-protein nitrogen amounting to 69 mgm., or over, per 100 cc of blood. As already noted above, the effects of myxedema, digitalis, myocardial degeneration and disease of the conduction system have been excluded so far as possible.

Exclusive of these complicating factors there were 12 of the 38 cases with abnormal changes in the electrocardiogram (other than abnormal axis deviation, sinus arrhythmia or tachycardia) which could not be wholly accounted for except by the consideration of a toxic effect of the products of uremia upon the heart muscle. Of the 12 positive cases none had a history of rheumatic fever or chorea and none showed physical signs of valvular heart disease. All had negative Wassermann reactions except 1 (serial No. 35, Table 1) and there was no history or physical sign of lues in this patient, who was aged twenty years. The greatest age in the positive group was forty-three years and the lowest twenty years, with an average age of thirty and one-half years. This makes arteriosclerotic heart disease unlikely as a causative factor in the production of these abnormal electrocardiograms.

Nine of the 12 cases received no digitalis either as determined by history or while in the Massachusetts General Hospital. One case (Serial No. 26) received the equivalent of 0.8 gm. of the dried digitalis leaf over a period of ten days and another case (No. 32) received 0.3 gm. over a period of seven days. The digitalis effect in both these cases we believe was negligible. Cohn³ found changes in the *T* wave in several cases after the equivalent of 0.6 to 0.8 gm. of the dried leaves of digitalis administered at the rate of 0.4 gm. daily, but the more usual amount found by him which was needed to produce changes in the *T* wave was 1.2 gm. in three days. A third case (No. 25) received the equivalent of 1.2 gm. of the dried leaves of digitalis in eleven days. This may have in part contributed to the change in form of the electrocardiogram but these changes were so marked that the record is included as undoubtedly the result in part at least of uremia.

TABLE OF 12 CASES OF UREMIA

Serial number.	Age.	Sex.	Edema.	Albuminuric retinitis.	Non-protein nitrogen.	Amount digitalis before Ecg.	Rhythm.	Auricular rate
13	42	M.	Feet and legs	+	Urea nitrogen 98 mg.	○	Normal	115
19	32	M.	Feet and legs	+	125	○	Normal	95
21	33	M.	Eyelids feet and legs	+	105	○	Normal	75
23	22	M.	○	+	83	○	Normal	98
25	43	M.	○	+	99 142 153	Total of 1.2 grams digitalis in 11 days	At first no evidence of auric. activity, auric. standstill and idioventricular rhythm. Later, probably auricular fibrillation and A-V rhythm. Still later (on day of death) a regular tachycardia, probably normal rhythm	
26	34	F.	Slight of feet	○	333	Total of 0.8 gram over a period of 10 days	Sino-auricular block with ventricular escape. Later varying from ectopic auricular rhythm to ventric. escape or to A-V rhythm	? 30 to 50 90 with ectopic auric. rhythm, otherwise 60
29	43	F.	○	○	201	○	Normal rhythm	80
30	35	F.	○	+	153 to 220	○	Sino-auricular tachycardia	115
31	22	M.	Marked general edema	○	69 38 one month later	○	a. Sino-auricular bradycardia? S-A block. b. After 1 month with marked improvement. Normal rhythm	40 65
32	43	M.	Ankles and sacrum	Papillo-dema both discs. Some exudate. Not typical albuminuric retinitis	174	0.3 gram over a period of 1 week	Sino-auricular block variable in Lead II every 4th beat. One dropped beat from A-V block in Lead III	Varying, 70 to 90
35	20	M.	○	+	70 to 111	○	Normal	90-100
36	21	F.	○	Fundi not examined	82	○	Normal	110

WITH ABNORMAL ELECTROCARDIOGRAMS.

Ventricular rate.	P-R interval.	Axis deviation.	P wave in Lead II.	Q-R-S complex.	T wave.
115	.16 sec.	Normal	P ₂ notched, +1	Normal	T ₁ - 1 mm. T ₂ flat. T ₃ + 1 mm.
95	.12 sec.	Normal	Normal	R ₂ + 30. Also ? intraventricular block	T ₁ - 2 + $\frac{1}{2}$ mm. T ₂ - 2 + 1 mm. T ₃ + 1 $\frac{1}{2}$ mm.
75	.15 sec.	Left, index +27	Normal	Normal	T ₁ - 1 mm. T ₂ - 1 $\frac{1}{2}$ mm. T ₃ + 1 mm.
98	.12 sec.	Normal	Normal	Normal high R ₂ + 25. mm., S ₂ - 8 mm.	T ₁ flat. T ₂ - 2 mm. T ₃ - 1 mm.
Varying, 55				At first right bundle branch block. Later left bundle branch block.	Varying as shown by plates from day to day:
45					a { T ₁ sometimes - 10 mm. sometimes - 5 + 5 mm. T ₂ - 2 + 2 $\frac{1}{2}$ mm. T ₃ + 9 to 10 mm. T ₁ begins high on downstroke of R, + 7 mm.
120 when regular	.2 sec. when P. is present	Slight left with regular rhythm. Index + 18	Small and notched when present	Still later reappearance of right bundle branch block	b { T ₂ Also begins high and is + 8 mm. T ₃ - $\frac{1}{2}$ to + 3 mm.
Regular at 55	.12 to .18 sec.	Left, varying from index + 20 to + 30	Varying, ? iso-electric. Best seen in Lead III, sometimes + 1 mm., sometimes - 1 mm. Later inverted and - 1 mm. in both rhythms.	Slurring of upstroke of R ₂	T ₁ flat to + 1 $\frac{1}{2}$ mm. T ₂ + 5 to + 6 mm. T ₃ + 5 mm.
Irregular at 80 or same as ectopic auric. rhythm	.2 to .05 sec. in A-V rhythm				
80	.15 sec.	Right, index - 20	Normal	Normal	T ₁ + 3 $\frac{1}{2}$ mm. T ₂ + 10 mm. T ₃ + 7 mm. Long S ₂ T ₂ interval.
115	.18 sec.	Left, index + 38	P ₁ notched	Wide, ? intraventric. block	T ₁ - 2 mm. T ₂ - 1 mm. T ₃ + 1 mm. Later (two days): T ₁ flat. T ₂ + 1 $\frac{1}{2}$ mm. Long S ₂ T ₂ interval T ₃ + 1 $\frac{1}{2}$ mm.
40	.18 sec.	Normal	P ₂ notched		a { T ₁ + 3-1 mm. T ₂ + 7 mm. T ₃ + 2 mm.
65			P ₂ normal	Normal	b { T ₁ notched + 1 mm. T ₂ broad + 1 mm. T ₃ flat.
Varying, 70 to 80	.12 sec.	Slight left, index + 18	P ₂ low, + $\frac{1}{2}$ mm. P ₃ - $\frac{1}{2}$ mm.	S ₂ + 8 and slurred	T ₁ + 4 mm. T ₂ + 7 mm. T ₃ + 4 mm.
90-100		Left, index + 19	Normal	Q-R-S normal	T ₁ - 1 to + 2 mm. (varying on different days) T ₂ - 2 to - 3 mm. T ₃ - 3 to - 5 mm.
110	.19 sec.	Normal	P ₂ notched, + 1 $\frac{1}{2}$ mm.	S ₂ and S ₃ deep and slurred ? intraventricular block	T ₁ + 4 mm. T ₂ + 6 mm. T ₃ + 2 $\frac{1}{2}$ mm.

Four of the 12 positive cases showed definite *abnormalities of rhythm*: (1) Probable auricular standstill and idio-ventricular rhythm, later changing to auricular fibrillation and in a few days to normal rhythm just before death; (2) sino-auricular block with ventricular escape, later varying from an ectopic auricular rhythm to ventricular escape or to atrioventricular nodal rhythm; (3) marked sino-auricular bradycardia, possibly sino-auricular block; (4) variable sino-auricular block and auriculo-ventricular block with rare dropped beats.

The heart rates were variable, and the bradycardia commonly said to be present in uremia was not commonly observed in our series. A *P-R* interval of 0.2 second or over occurred in 2 cases. One of these cases had had digitalis as already discussed (Case No. 25). The *P* wave in Lead II was small and notched in four instances.

In 4 cases there was abnormality of the *QRS complex* indicating definite intraventricular block in 1 and probable intraventricular block in the other 3.

The *T wave in Lead II* was flat, diphasic or inverted in 7 of the 12 positive cases and unusually high (+ 5 mm. or greater) in the other 5 cases. In case No. 25 the *T* showed various queer forms, sometimes originating high on the downstroke of R_2 (see Fig. 4). In case No. 31 when the patient was quite sick shortly after admission to the hospital, the T_2 wave was + 7 mm. With the patient's gradual recovery the T_2 wave dropped to + 1 mm. Pronounced left axis deviation with an "index"⁶ of + 18 or greater was present in 6 of the 12 positive cases; abnormal right axis deviation occurred only once.

Of these 12 cases with abnormal electrocardiograms 5 had slight to marked edema of the feet and legs and 1 had marked generalized edema. Seven had definite albuminuric retinitis; 3 showed normal fundi, was doubtful, and 1 was not examined. In 8 of the 12 cases a phenolsulphonephthalein kidney test was done; 4 showed no output in two hours and ten minutes; 2 showed 10 per cent or less and 2 showed 25 per cent in two hours and ten minutes; 7 had a hemoglobin reading of 75 per cent or less. All except 1 (Case No. 36) had the typical urinary findings of advanced nephritis. The systolic blood-pressure varied from 115 to 245 mm. of mercury with an average systolic blood-pressure of 202 mm. of mercury. The diastolic pressure varied from 82 to 160 mm. of mercury with an average of 132 mm. of mercury. In 11 of the 12 cases with abnormal electrocardiograms the non-protein nitrogen varied from 69 mgm. to 333 mgm. per 100 cc of blood, and 1 case (No. 13) had a urea nitrogen of 98 mgm. per 100 cc of blood. Of the 12 cases showing abnormality of electrocardiograms partially or wholly due to the toxic effects of uremia on the heart muscle, 11 died under hospital care and 1 was discharged "apparently improved."

There were 8 of the 38 cases of uræmia studied, uncomplicated by heart disease or digitalis, which failed to show abnormality of the electrocardiogram. Two of these presented edema of the feet and legs and 1 showed rather marked edema of the face, thighs and legs. Three presented definite albuminuric retinitis, 3 showed normal fundi and in 2 the fundi were not examined. Five had no phenolsulphonaphthalein excretion in the urine in two hours and ten minutes, 1 had a 25 per cent excretion and 1 a 50 per cent output. All of these 8 cases showing no abnormality of the electrocardiogram had a hemoglobin reading of 75 per cent or less. The systolic blood-pressure varied from 110 mm. of mercury to 210, with an average systolic pressure of 168 mm. of mercury. The diastolic pressure varied from 60 to 145 mm. of mercury and averaged 106.6 mm. of mercury. In 7 of the 8 cases where the determination was made, the non-protein nitrogen varied from 70 mgm. to 210 mgm. per 100 cc of blood, an average of 135.5 mgm. per 100 cc of blood. A comparison with 11 of the 12 positive cases in which a blood non-protein-nitrogen determination was made shows in the 11 positive cases a variation from 69 mgm. to 333 mgm. per 100 cc of blood and an average non-protein nitrogen of 143.4 mgm. per 100 cc of blood. The difference between the two groups is not striking enough and the cases not numerous enough to draw any conclusions. Finally, of the 8 cases of uræmia failing to show abnormalities of the electrocardiogram 3 died under hospital care, 1 was discharged in "poor condition" and 4 were discharged temporarily "improved."

A review of these studies fails to show a common factor in either positive or negative group and the nature of the toxin causing the change in the heart muscle as well as any common factor is obscure. In general the positive cases seemed to have a more advanced nephritis, as apparently indicated by the hospital mortality, albuminuric retinitis, higher blood-pressures and apparently the greater incidence of edema. At present it is not possible by history, physical examination or laboratory findings to predict which cases of uræmia will show abnormal changes in the form and direction of the electrocardiographic complexes.

A relatively high blood-pressure with a probable resulting hypertrophy occurred in most of the cases studied and left axis deviation occurred in 6 of the 12 positive cases, though not marked. These might be considered as possible factors in the changes produced in the *T* wave in some instances. However, a study of 14 cases of marked left-axis deviation, with an "index"⁶ of from + 30 to + 45, showed the *T* wave in Lead II to be normal and upright in every instance. Twelve of these had *T*₂ waves of + 1½ mm. to + 5 mm. Two had *T*₂ waves of + 1 mm., 1 of these having received an appreciable amount of digitalis. In this group the systolic blood-pressure varied from 115 mm. of mercury to 270 mm.

of mercury and the average was 185.8 mm. of mercury. The diastolic pressure varied from 70 to 150 and averaged 107.5 mm. of mercury.

Two cases of severe diabetic coma showed no abnormality of the electrocardiogram other than a tachycardia, the T_2 wave being upright and normal.

Three cases showing abnormal electrocardiograms are presented in brief here.

Case Report.—CASE I. C. C., a single man, aged twenty years, a checker in a rubber factory, entered the Out-patient Department of the Massachusetts General Hospital, January 17, 1923, complaining of rapid loss of vision.

About two and a half years before entrance the patient was found to have chronic nephritis at another hospital. This was discovered following an attack of influenza. He was unable to get insurance at this time because of the albumin in his urine. For two years he had practically no symptoms except severe "morning" headache occurring about once a week. There was complete absence of dyspnea and of edema of the feet. Three weeks before entrance to the Massachusetts General Hospital his vision started to fail and became progressively worse. He entered the hospital for this reason.

The past history reveals no story of rheumatic fever, chorea or scarlet fever. The tonsils were definitely bad in childhood and were removed at the age of eleven years. The past history was otherwise negative. There was no history or physical sign of venereal disease.

On *physical examination* the presenting features were as follows: a muddy pallor, an uremic breath, marked albuminuric retinitis and slight cardiac enlargement. The apex impulse of the heart was in the fifth interspace 8 cm. to the left of the mid-sternal line, and the mid-clavicular line was 7.5 cm.—very slight enlargement to the left clinically. There were no murmurs and no abnormalities of rhythm.

The blood-pressure was observed 4 times over a period of two months and the systolic pressure varied from 210 to 240 mm. Hg., and the diastolic pressure from 140 to 170 mm. Hg. The urine showed a large amount of albumin, granular casts and 6 to 12 red blood cells per high-power field. The non-protein nitrogen was taken 7 times in two months and varied from 70 to 111 mgm. per 100 cc of blood.

The patient was ambulatory although in a state of chronic uremia from January 17, 1923, to March 14, 1923, and was examined frequently in the hospital. After the latter date he was unable to come in but was confined to his bed at home with frequent vomiting attacks. Convulsions finally occurred and the patient died June 23, 1923, in uremic coma.

Discussion. A young man with chronic uremia was observed over a period of two months and blood nitrogen determinations were made and electrocardiographic plates taken. He received no digitalis at any time. There were never any signs of cardiac failure and cardiac

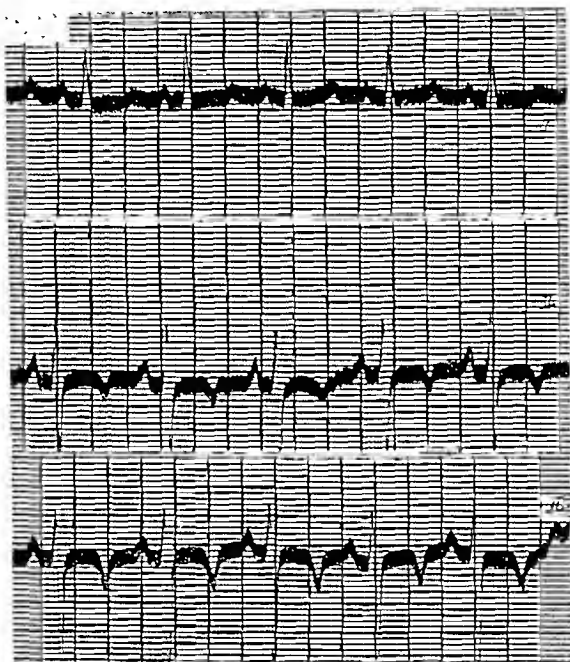


FIG. 1.—Electrocardiogram of C. C., taken January 31, 1923. Normal rhythm; inverted *T* in Leads II and III; slight left axis deviation.

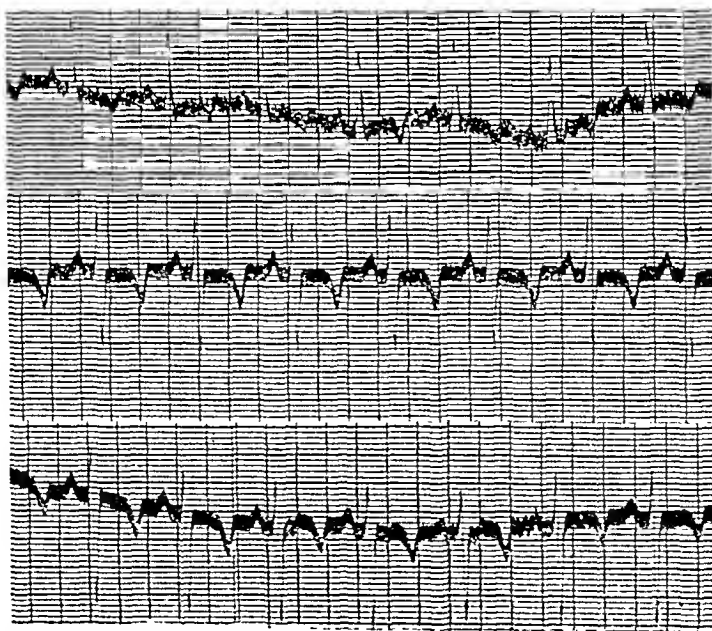


FIG. 2.—Electrocardiogram of C. C., taken February 17, 1923. Normal rhythm; inverted *T* in Leads II and III; inversion of *T* in Lead II is more marked than in Fig. 1. Also *T* in Lead I is now inverted.

hypertrophy was only slight clinically. The *T* wave of the electrocardiogram in Lead II was definitely abnormal and was constantly inverted (See Figs. 1 and 2). The toxic effect of the uremia upon the heart muscle was probably the cause of this. The degree of inversion of the *T* wave bore no constant relation to the blood non-protein nitrogen.

CASE II. G. S., a marine engineer, aged forty-three years, entered the Massachusetts General Hospital November 10, 1921, complaining of dyspnea. The symptoms were frontal headache and increasing dyspnea and weakness for eighteen months.



FIG. 3.—Electrocardiogram of G. S., taken November 18, 1921. Intraventricular block; no evidence of auricular activity; question of auricular standstill and idioventricular rhythm; varying ventricular complexes; *T* wave in Lead I varies from diphasic to inverted, according to shape of *Q R S*.

There was no history of rheumatic fever or chorea. No history or physical sign of venereal disease was present. The patient had received a total of the equivalent of 1.2 gm. of the dried digitalis leaf over a period of eleven days just before entrance. He received no digitalis while in the hospital.

The presenting symptoms and signs were stupor, cyanosis, albuminuric retinitis and medium moist rales at both lung bases posteriorly. The heart was markedly enlarged to both the right and left; the sounds were of fair quality and no murmurs were present. The systolic blood pressure was 200 mm. Hg. and the diastolic was 100 mm. Hg.

The urine showed a specific gravity of 1010 to 1012, a large amount

of albumin and occasional granular casts and white blood cells in the sediment. The non-protein nitrogen varied from 99 mgm. to 153 mgm. per 100 cc of blood. The blood Wassermann reaction was negative.

The patient grew steadily worse. The uremic symptoms became more marked, pericarditis with effusion developed and he died November 26, 1921.

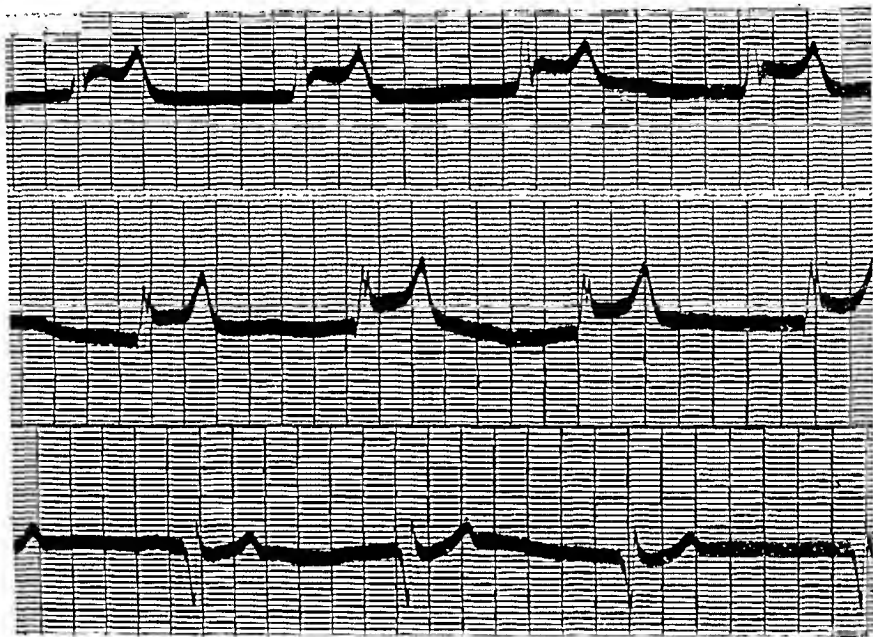


FIG. 4.—Electrocardiogram of G. S., November 22, 1921, still showing no evidence of auricular activity. Intraventricular block persists and the *T* wave in Lead II is high and now originates from the downstroke of the *Q R S* complex.

Discussion. The bizarre and rapidly changing electrocardiographic complexes (Figs. 3 and 4) cannot be explained by the ingestion of the equivalent of 1.2 gm. of digitalis leaves over a period of eleven days. Neither does hypertensive heart disease afford a complete explanation. The toxic effect of uremia on the heart muscle must be considered as the most likely explanation of the changes of the *Q R S T* waves. Digitalis may have been an additional factor.

CASE III. G. E., a white man, aged forty-three years, a druggist, entered the Massachusetts General Hospital, January 16, 1923, semistuporous with marked hyperpnea.

The patient had not been sick up to the present illness, which began two weeks before entrance with dyspnea on exertion. This gradually increased until he was obliged to go to bed. Three or four days before entrance his ankles began to swell and he began to grow drowsy. There had been some increase in urinary frequency

for two months, with nocturia once to twice a night during this period.

There was no history of scarlet fever, diphtheria, rheumatic fever or chorea during childhood. The past history was entirely negative so far as could be found out.

On examination the patient was pale, semistuporous, markedly hyperpneic and had a heavy urinous odor on his breath. Examination of the fundi showed papilledema, several small hemorrhages and one or two small spots of exudate on each side. Ascites was present; there were moist rales at both lung bases. There was marked edema of the ankles and over the sacrum.

Examination of the heart showed a left border of dulness of 11 cm. with a right border of 4.5 cm. and a midclavicular line of 8 cm. The heart sounds were irregular, slow and almost obscured by a loud to and fro friction rub. The radial and brachial arteries were thickened and tortuous. The blood-pressure was difficult to determine; the pulse beats came through very irregularly; the highest, a few beats, appeared below the cuff at 185 mm. mercury; all beats appeared at 140 mm. mercury; the diastolic pressure was 120 mm. mercury.

No urine specimen was obtained. The non-protein nitrogen was 173.5 mgm. per 100 cc of blood. The blood hemoglobin was 60 per cent and the red count was 2,370,000. Two Wassermann reactions proved to be negative.

The patient gradually became more stuporous, his respirations became slower and he died January 17, 1923, after one day in the hospital.

Subsequent autopsy showed a heart weighing 615 gm. with a normal looking myocardium. Acute pericarditis was present. There were no valvular lesions. Other findings were arteriosclerosis, arteriosclerotic nephritis, infarct of right lung, small infarcts of kidneys, right hydrothorax, slight ascites, chronic passive congestion, edema of legs and feet and ulcerative colitis.

Discussion. A man, aged forty-three years, with no evidence of syphilis, but quite toxic from advanced uremia, showed an unusual cardiac arrhythmia by electrocardiogram. Hypertension and cardiac hypertrophy with failure were present and also peripheral arteriosclerosis but there was no history of anginal failure. The arrhythmia was apparently due to a sino-auricular nodal depression with sino-auricular block (Fig. 5). Neither hypertensive heart disease nor arteriosclerosis explain this. The latter particularly is more likely to interfere with auriculo-ventricular conduction. The arrhythmia here is more likely due to a toxic effect of the uremia on the sino-auricular node. The equivalent of 0.3 gm. of powdered digitalis leaf over a period of seven days is not sufficient to produce such a toxic effect on the heart. Both the sino-auricular nodal depression and the

unusually high *T* in Lead II are best explained by the effect of the toxic products of uremia on the heart muscle (perhaps somewhat increased by digitalis).



FIG. 5.—Electrocardiogram of G. E., January 16, 1923, showing sino-auricular block, every fourth beat "dropped" in Leads II and III. High *T* in Lead II and slight left axis deviation.

Conclusions. In certain cases of uremia and severe nephritis with an increased blood nitrogen there is a toxic effect acting in some respects like digitalis on the heart muscle. It may produce abnormal electrocardiograms: changes in the *T* wave of Lead II, less often abnormal rhythm, and rarely an increase in the auriculo-ventricular conduction interval* or in the duration of the *Q R S* complex.

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* Through the kindness of Dr. A. L. Barach of New York City we have received data concerning the electrocardiograms of a series of 20 cases of uremia observed by him. Seven of these cases were digitalized. Of the remaining 13, 8 showed diphasic or inverted *T* waves in lead II,

THE VASCULAR CHANGES OF THE KIDNEY IN HYPERTENSION.

BY R. H. JAFFE, M.D.,

CHICAGO.

(From the Department of Pathology of the University of Illinois, College of Medicine, and the Uihlein Memorial Laboratory of the Grant Hospital of Chicago.)

THE microscopical examination of the kidneys of individuals who have suffered from hypertension reveals different findings. In a certain group of cases named primary hypertension or hyperpiesis, no changes are found in the kidneys (Allbutt,¹ Keylin,² Lec,³ v. Monakow,⁴ Moschcowitz,⁵ Ophuels,⁶ Vey and Allbutt⁷). This is in accordance with the clinical statement that in this group the renal function has proved normal (Strouse and Kelman⁸). More frequently, however, high blood-pressure and hypertrophy of the heart are associated with diseases of the kidneys. Apart from the different forms of glomerulonephritis, there are numerous cases in which the most striking feature is a sclerosis of the small renal arterics. The intensity of the arteriosclerosis is a very variable one. By comparison all stages can be found, from a slight thickening of the wall with insignificant effect on the parenchyma, to a hyaline occlusion of the majority of the renal arterioles followed by obliteration of the glomeruli, atrophy of the tubules and proliferation of the interstitial connective tissue. This sclerosis finally results in the well known clinical and anatomical picture of the primary contracted kidney (Gaskell,⁹ Herxheimer,¹⁰ Jores,¹¹ Loehlein¹²).

The question has frequently been discussed, whether the hyperplastic and degenerative changes observed in hypertension in the small arteries of the kidney are confined to this organ or whether other organs are also involved. Since the work of Gull and Sutton, the sclerosis of the renal arterioles has often been considered part of a universal arteriolar fibrosis (Jores, Moschcowitz, Muenzer¹³). Certain objections against a generalization of this assumption can be made, for there are undoubted cases of sclerosis of the small arteries confined to the kidney (Evans,¹⁴ Herxheimer, Hecht, Loehlein). Where arteriosclerosis is found in the spleen, as well as in the kidney, it must be kept in mind that in this organ, arteriosclerosis is an almost physiological occurrence in the adult after forty to fifty years of age, (Herxheimer, Matsuno). In the cases with a more universal arteriosclerosis, the process in the kidney as a rule is more advanced and more pronounced than in brain, liver, testis, etc. Only in the kidney is this alteration followed by a well-characterized destruction of the parenchyma, whereas it is absent in the other organs just mentioned. In the pancreas,

however, the changes in the small arteries are sometimes almost as severe as in the kidney (Aschoff,¹⁶ Herxheimer, Moschcowitz, Schwab¹⁷); here too, they may cause atrophy of specific tissue (islets), with clinical signs of disturbed function (diabetes—Hoppe-Seyler¹⁸).

It can be stated, therefore, that the small arteries of the kidney, in particular, are disposed to sclerosis. This local disposition may be partly due to the intricate vascular system of this organ apparently favoring circulatory disturbances, which, if they lead to an increase of the intravascular pressure, will cause changes in the vessels.

Can we observe changes in the arterio-capillaries of the kidney that will permit the conclusion that distinct circulatory disturbances exist? They should be sought only in cases of hypertension that are not far advanced. In the later stages, when the pathological process has advanced, the first and most characteristic consequence of an altered blood-flow will be overshadowed by secondary alterations. In other words, what are the presclerotic changes in the kidney.

Loehlein described marked dilatations of the arterioles preceding the sclerosis. According to him, the presclerotic dilatation gradually passes over to the thickening and degeneration of the arterial walls of the later stages. Loehlein's observation has been confirmed by Fahr. These two authors give no explanation for their findings.

During several years I have collected kidneys obtained in post-mortems of cases with hypertension. In the present paper, the very beginning of the renal sclerosis will be mainly discussed.

From my collection I have chosen 5 cases of clinical hypertension of short or moderate duration. The determination of the exact time of onset is, of course, impossible because of the insidious character of the process, but a short review of the cases will indicate why I have selected these to illustrate the points under discussion. All 5 are males.

Case Abstracts. CASE I.—Aged twenty-seven years; sudden death.

Postmortem Findings. Heart 400 gm.; the opening of the left coronary artery closed by a fresh thrombus, $1 \times \frac{1}{2}$ cm. in diameter. At the place where the thrombus was attached to the wall of the aorta, the intima showed slight fatty degeneration. Kidneys macroscopically normal.

CASE II.—Aged twenty-nine years; physician; smoked 60 to 100 cigarettes daily; he noticed that his blood-pressure was high (systolic 180) half a year ago; died suddenly.

Postmortem Findings. Heart 395 gm.; thrombosis of the left coronary artery; isolated sclerosis of the left coronary artery; kidneys hyperemic, of normal size and form.

CASE III.—Aged forty-five years; diabetes mellitus; systolic blood-pressure 190; no albuminuria; death in coma diabeticum.

Postmortem Findings. Heart, 390 gm.; pancreas 33 gm; extensive lipomatosis; kidneys (together), 302 gm.; cloudy swelling; slight hyperemia.

CASE IV.—Aged thirty-five years; symptoms of gout for a few months; systolic blood-pressure 200; died of influenza-pneumonia within twenty-four hours.

Postmortem Findings. Heart, 405 gm.; hemorrhagic pneumonia of the right lung; kidneys more consistent than normal and hyperemic.

CASE V.—Aged thirty-five years; house painter; blood-pressure 225. Clinical diagnosis: Chronic lead-poisoning; primary hypertension; hemorrhage of brain.

Postmortem Findings. Heart, 557 gm.; thrombosis of the arteria basilaris cerebri; distinct sclerosis of the basal arteries of the brain; kidneys firm, smaller than normal (weight together 215 gm.), surface smooth.

Microscopical Examination. Examining the tissues of Case I microscopically, I first had the impression that the kidneys were normal; but later I changed my opinion, after I had learned, by comparison with other cases, to recognize an alteration which at first sight was not very striking. This was a slight and circumscribed dilatation of the afferent arterioles. Also in Cases II, III, and IV, the lumen of the vasa afferentia was distended more distinctly, especially in Case III.

As shown in Fig. 1, the dilatation begins at the hilus of the glomerulus. The short intraglomerular part of the arteriole, which normally forms a small ampulla, is at first widened. Later, the whole vas afferens is dilated (Fig. 2).

In the earliest stage, the structure of the vascular wall apart from the distension is not affected. As the alteration proceeds, the walls become thicker by proliferation of the cells of the intima and enlargement of the cells of the media (Fig. 3). Hyaline masses appear under the endothelium (Fig. 2). They spread out over the intima and to the adjacent part of the media. Finally the vascular coats are completely involved, while the lumen becomes markedly narrowed. This stage was reached in Case V (Fig. 4).

In the other organs—brain, pancreas, liver—no sclerosis and no dilatation of the smallest arteries was found. This excludes the possibility that the dilatation of the renal arterioles is merely a part of a universal passive congestion. Besides, in this condition the vasa efferentia with the tufts of the glomeruli and the veins are distended, but not the vasa afferentia.

The isolated dilatation of the afferent arterioles of the kidney in

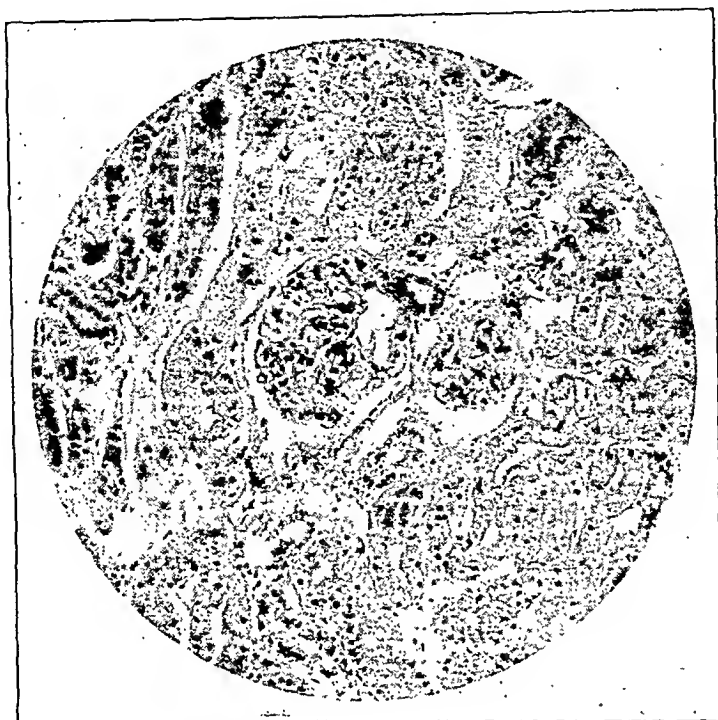


FIG. 1.—Dilatation of the intraglomerular part of the vas afferens. Irregular blood content of the tufts. Beginning hyaline degeneration of their wall (Case III).

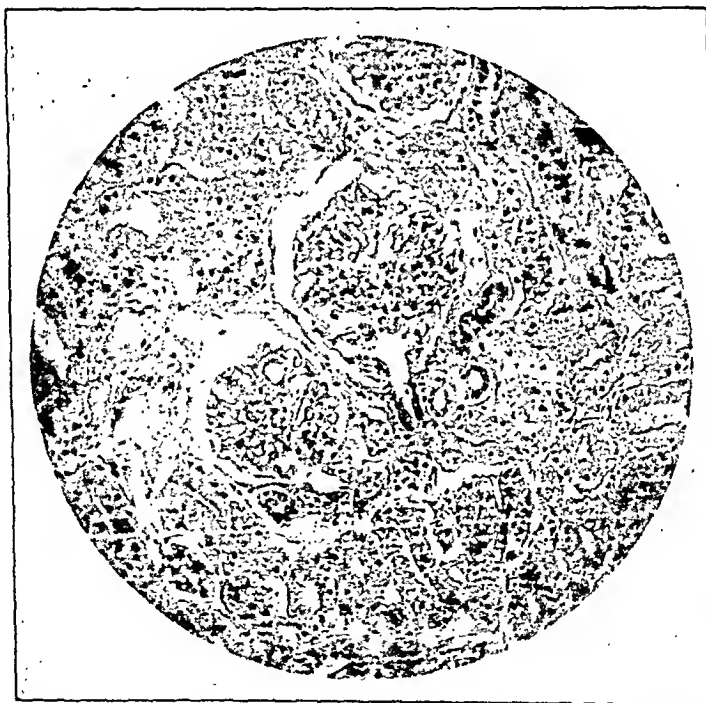


FIG. 2.—Dilatation of the vas afferens with hyaline degeneration of the intima. Irregular blood content and more advanced hyaline degeneration of the tufts (Case III).

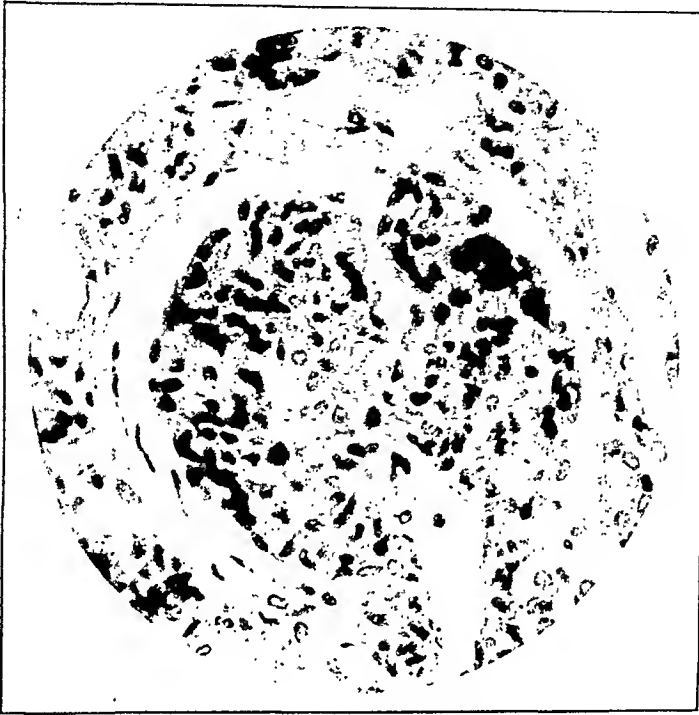


FIG. 3.—Dilated vas afferens with proliferation of the cells of the wall. Thickening of the Bowman's capsule (Case IV).



FIG. 4.—Hyaline sclerosis of the vas afferens with pronounced narrowing of its lumina (Case V).

early hypertension is interesting because it indicates not only disturbances in the renal circulation, but it points to a certain place where the disturbances may arise.

When we find a circumscribed dilatation of a portion of a vascular system without structural alteration of the wall, we must assume that a narrowing of the lumen has occurred at a point beyond the dilatation with a resulting increase in the pressure in the proximal portion. Such pressure distends the wall.

Distal to the vasa afferentia are the tufts of the glomeruli. The splitting up into the numerous tufts produces a sudden and considerable increase in the vascular capacity. Under normal conditions we should therefore anticipate no resistance to the circulation at this point.

Are changes to be found in the tufts of the glomeruli in the pre-sclerotic stage? According to Loehlein, the glomeruli are normal at this time.

Case I of our series seemed to confirm Loehlein's statement, for no alterations of the glomeruli were noted. In the other cases, however, the glomeruli could not be called normal. Irregularities were found in the blood content of the loops, and in the same glomerulus, some tufts were filled by blood, while others were empty and narrowed. The capillary walls appeared to be thickened and less distinctly stained. In Case III these irregularities were well pronounced and combined with circumscribed hyalinization of the capillaries (Figs. 1 and 2). In Case IV, thickening of Bowman's capsules was also observed, (Fig. 3). We are therefore able to state that in the early stages, in which the vasa afferentia are dilated, changes in the glomeruli may be seen. These changes, called by Moschcowitz "arteriosclerosis en miniature," cannot be considered as resulting from the sclerosis of the arterioles, as was done by several authors; first, because the hyalinization is sometimes more advanced in the tufts of the glomeruli than in the afferent vessel, and secondly, because in the beginning there is often no connection between the degenerated parts of the glomerular capillaries and the arterioles. Thus, the hyaline thickening is quite frequently found first at the top of a tuft. Evans and Dunn also are inclined to regard the glomerular changes primary to those of the small arteries. It is not to be denied, of course, that the narrowing and the occlusion of the lumen of the vasa afferentia, found in the later stages of genuine atrophy of the kidney, means severe damage to the glomeruli (Jores, Loehlein).

The hyalinization of the capillaries just described, cannot form the real cause for the increase of pressure within the arterioles, for it was absent in Case I, though the afferent vessels were distended. But, in my opinion, the sclerosis of the tufts indicates a direct injury to the glomeruli. It is very likely that this injury first leads to contractions of the capillary tufts without destruction of their wall.



FIG. 5.—Necrosis of renal arterioles in syphilis.

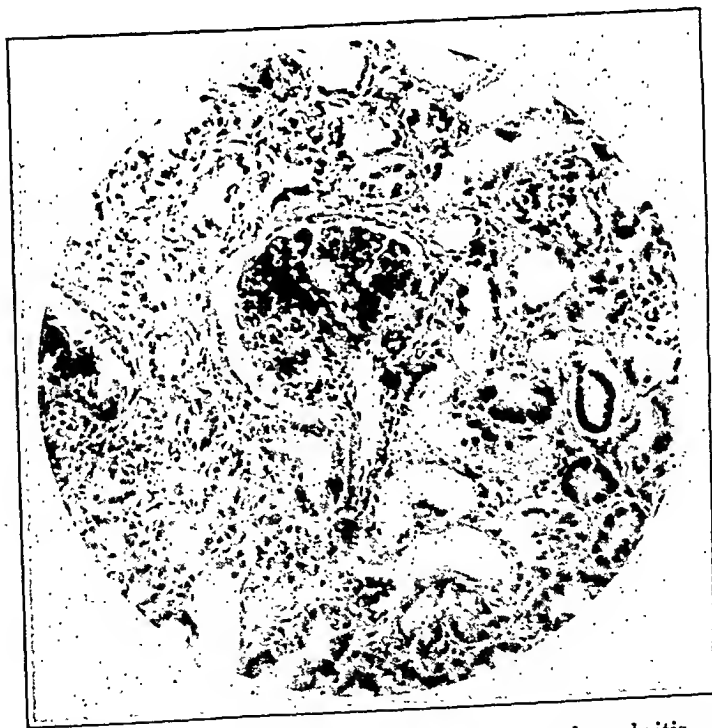


FIG. 6.—Dilatation of the vas afferens in chronic glomerulonephritis. Man, aged forty years. Heart: 465 gm. Secondary contracted kidney.

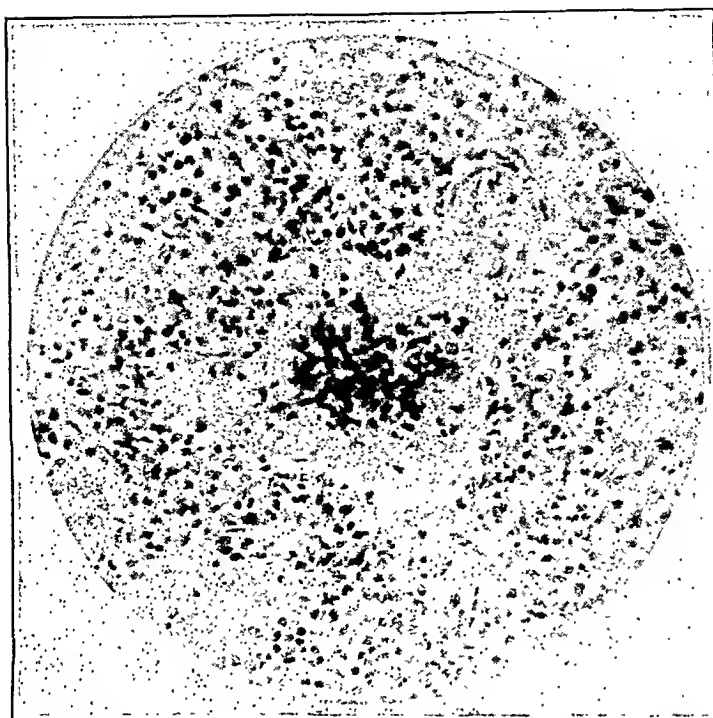


FIG. 7.—Arteriolitis with necrosis in subacute glomerulonephritis. Man, aged twenty-six years. Heart: 385 gm.

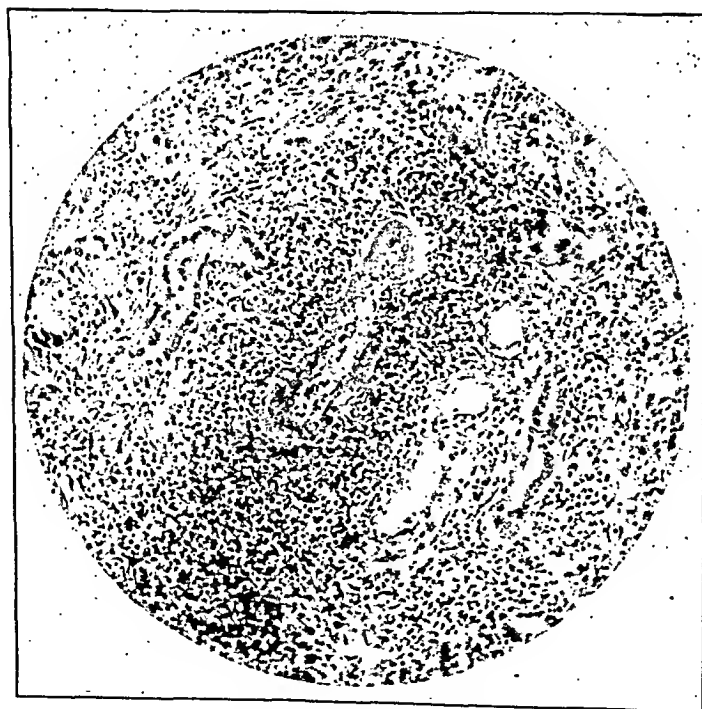


FIG. 8.—Very severe arteriolitis in acute exacerbation of chronic glomerulonephritis.

If the injury continues and the spasm is frequently repeated, visible changes will finally result in the capillaries.

By contraction of the tufts the blood flow through the glomeruli will be interrupted. The irritating agent, held back by the spasm in the capillaries, will accumulate in the arterioles, bringing about here the effort of contraction and this against an increased resistance. As the muscular coat of the vasa afferentia are too insignificant to compensate successfully for this increase in work, other parts of the circulatory system will react to keep up the renal circulation, and at the point of resistance, the thin walls of the afferent arterioles will be distended. This explanation presupposes the existence of an independent contractility of the capillaries.

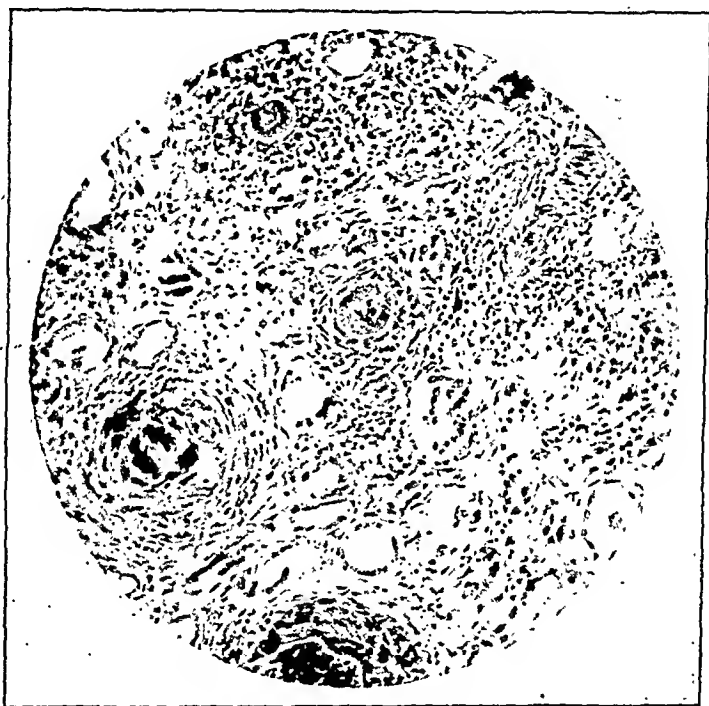


FIG. 9.—Arteriolar sclerosis in the same kidney as Fig. 8.

Extensive investigations made during the last few years seem to have proved beyond doubt that the capillaries may contract and dilate without any influence from the vessels between which they are intercluded. For details, reference should be made to the fundamental works of Krogh,²⁰ Dale,²¹ Ebbecke,²² Cotton, Shade and Levin,²³ and Mueller.²⁴ Most of this work has been carried out on the capillaries of the skin, which may readily be studied during life. Relations between the capillaries of the skin and those of the kidney have also been suggested (Weiss,²⁵ Schlayer,²⁶ Eskil Kylin²⁷). Direct observation of contractions of glomerular capillaries in the frog kidney has recently been reported by Richards.²⁸

Though an independent contractility of the glomerular capillaries in man has not yet been directly proved, these observations, combined with the microscopical findings in the renal arterioles in early hypertensions, give strong support to its existence. The capillary spasm will first affect the circulation of the kidney. But the sudden and repeated elimination of an important part of the circulatory system will not remain without effect on the heart. Its reaction against the increased resistance will be an increased action. Hence the blood-pressure will rise.

In explaining essential hypertension, spasmodic contractions of the peripheral vascular structure, especially of the small arteries, have been frequently emphasized (Monakow, Pal,²⁹ Schlayer, Strouse and Kilman, Volhard,³⁰ Warfield). With regard to the kidney, the isolated dilatation of the vas afferens, as found in early hypertension, rather suggests spasms of the tufts than of the arterioles.

The arterio-capillary contractions may not be confined to the kidney, for they may also occur in other parts of the body. It will easily be understood, that disturbances mainly in the renal blood flow may play an important role in altering the blood-pressure, when we consider the rich blood supply and great functional activity of this organ (v. Monakow, Warfield).

While it is supposed that capillary contractions cause the rise of the arterial pressure, the dilatation of the vas afferentia is to be regarded as resulting from the hypertension. Does the latter also produce the sclerosis which follows the dilatation?

The theory has been brought forward that arteriolar sclerosis arises from hypertension by Allbutt, Faber, Moschcowitz,³³ and others. But the height of the blood-pressure does not correspond to the intensity of the vascular degeneration. There are cases showing the same increase of the pressure, but the changes in the renal arterioles are widely different. Severe hyaline and lipid destruction of the small arteries is sometimes found combined with a blood-pressure and a weight of the heart less than in benign vascular sclerosis of the kidney. A type of renal arteriosclerosis is characterized by a blood-pressure which is almost normal (Ophuels, Lichtwitz³²).

Therefore, we cannot but assume that certain irritants directly affect the vessel wall. It is very likely that such substances are those which cause the spasm of the glomerular tufts, and accumulate in the precapillary part. On the intensity of the direct irritation will depend the extent of the sclerosis.

As to the nature of this irritant, attention is directed in this connection to lead and nicotine³⁴ (Cases II and V), both of which are known to induce vascular contractions. One needs but to recall the arterial spasm of lead colic; and, according to Naegeli,³⁵ the paleness of lead miners is usually due to vascular spasms in the skin, and not to anemia,

The relative frequency of genuine atrophy of the kidney in cases of diabetes and gout, indicates that toxins affecting the small arteries are produced in disturbed metabolism. The nature of these toxins has not yet been defined. Aufrecht³⁶ suggests, from his studies in guinea-pigs, that the abnormal concentration of uric acid is injurious to the arterioles. In a series of experiments, I injected solutions of mono-sodium urate intravenously into 5 rabbits, each receiving 5 to 10 mg. of urate daily for four to six weeks. There were no symptoms of disturbed kidney function to be observed. In the urine, albumin and casts were absent, and the urea, non-protein nitrogen- and creatinin-content of the blood was normal. The uric acid soon disappeared. The rabbits were killed later. The kidneys showed no pathological changes. These experiments, however, have no bearing on disturbances of the purin metabolism in man, the latter being so different in this regard from the small rodents used in laboratory work.

In some cases relations have been suggested between cardio-renal diseases and disturbances of the internal secretion (thyroid, A. Fischberg³⁷) Munk and Newburgh,³⁸ emphasize the deleterious influence on the arterial wall of diets rich in proteins.

May hypertension and arteriolar sclerosis result from injuries of an infectious nature? Goepp,³⁹ made reference to the possibility of focal infection being responsible for a certain number of cases of hypertension. The theory has been advanced by several investigators (Klotz, Ophuels), that in arteriosclerosis an inflammatory factor participates. Ophuels lays stress upon the close etiological relationship between infection and arteriosclerosis. I have seen typical genuine atrophy of the kidney connected with chronic tuberculosis of bone.

Fahr and Meyer⁴⁰ have described in primary contracted kidneys very severe alterations in the small arteries, with necrosis and inflammatory destruction of the vascular wall. According to these authors, syphilis and rheumatic arthritis play an important role in the etiology of these cases.

In Fig. 5 such severe changes in the renal arterioles are shown. These appeared in a man, aged thirty years, who came to the hospital complaining of shortness of breath and pains in his chest. He admitted a syphilitic infection about three years ago. The Wassermann test was strongly positive. His systolic blood-pressure was 200. Albumin and many waxy casts were found in the urine. The patient died suddenly of heart insufficiency before an exact clinical examination had been made. The postmortem revealed: Hypertrophy of the heart, (weight 480 gm.); severe sclerosis of the coronary arteries; no atheroma in the aorta. Spleen: weight 204 gm., Kidneys: weight, 100 gm., with surface coarsely granulated, cut surface pale, grayish-red, structure less distinct and consistency increased. In the microscopical examination of the kidneys,

hyaline and lipoid degeneration of the arterioles was found. Some small arteries were necrotic with structureless walls. There was only a slight inflammation around the necrotic vessels. Many glomeruli revealed hyaline degeneration. In some of the remaining glomeruli, necrosis of single loops was seen.

The histological picture of this kidney fully resembles Fahr's and Meyer's descriptions. But I hesitate to include these changes in the groups of sclerotic diseases of the kidney. There is certainly not always a definite demarcation between arteriosclerosis and inflammation. A cellular reaction, however, like that described, ought rather to have been recorded as specific arteritis than as arteriosclerosis (Cp. Aschoff).

Affections of the renal arterioles, similarly intensive sometimes occur in glomerulonephritis. In this connection, a brief discussion of the findings in the small arteries in nephritis may be of interest. Here we deal with an evident obstruction of the glomerular circulation by the inflammatory reactions within the tufts. Does this obstruction lead to vascular changes like those described in hypertension?

From numerous studies it is known that in cases of nephritis the vasa afferentia are often altered (Gaskel, Loehlein, Dyke⁴¹). Aufrecht⁴² and Elwyn,⁴³ therefore, emphasize the importance of these as primary lesions in these diseases. Aufrecht described thickening of the wall, swelling of the nuclei of the muscle cells, and an increased number of cells in the adventitia. Ophuels called attention to an early subendothelial thrombosis of the small arteries, followed by fibrosis as a result of organization. Loehlein mentioned the fact that the vasa afferentia were often dilated. In 10 to 20 per cent distinct alterations of the walls were present. He found necrosis and formation of small aneurysms. Loehlein's observations were confirmed by Fahr. Baehr and Sacks⁴⁴ have seen severe lesions in the small arterioles occurring in diffuse glomerulonephritis combined with verrucous endocarditis. Bell and Hartzel⁴⁵ mentioned thrombosis of the affected arterioles.

In 94 cases of acute and subacute glomerulonephritis which I examined, dilatation of the vasa afferentia was very common. Sometimes this was of moderate extent, occasionally very pronounced (Fig. 6). The resemblance of the dilated vasa afferentia in Figs. 2 and 6 is very striking. In Fig. 6 the tufts of the glomeruli are distinctly closed by inflammatory changes in their wall. Five times I observed very marked alterations of the arterioles. They were necrotic, surrounded by leukocytes and lymphocytes which invaded the structureless wall and filled the lumen (Figs. 7 and 8). This arteriolitis could not be due to mechanical injury (stasis, pressure), but must be the result of a distinct toxic irritation.

In the chronic forms of glomerulonephritis (secondary contracted kidney), hyperplastic sclerosis is frequently found in the small

arteries. Lochlein separates this sclerosis from the acute arteriolitis. The former is considered by him as due to the high blood-pressure. But the increased pressure cannot in itself produce the vascular change, for we see cases of chronic glomerulonephritis with sclerotic arterioles and without hypertrophy of the heart (Evans).

In the kidney from which Fig. 6 was taken, there were, besides the acute inflammatory changes, older processes that showed more or less advanced obliteration of the glomeruli, and atrophy of the tubules. The different age of the inflammatory attacks was very marked. A typical hyaline sclerosis had developed in the areas of chronic inflammation (Fig. 9), while the arteriolitis was confined to the areas of acute inflammation. This can be explained on the assumption that the arteriolitis and the sclerosis were produced by similar causal agents, the former being the result of a very intensive and acute toxic alteration; the latter being due to a less severe and chronic affection.

From these observations a distinct resemblance of the vascular changes in the primary sclerosis of the kidney to those in nephritis can be determined. This is the reason why the two conditions, though different in their nature, have often been confused. The resemblance lends support to the theory I have advanced above in an effort to explain the genesis of the isolated renal arteriosclerosis in hypertension.

Conclusions. No satisfactory explanation has yet been given for the frequent coincidence of hypertension, hypertrophy of the heart, and sclerosis of the small arteries of the kidney. That the sclerosis may cause the rise of the blood-pressure by increasing the resistance in that part of the circulation has been denied. Of the objections brought forward against this theory, the most important one is that hypertension may occur though the renal arterioles show no thickening of their wall. For these reasons it was thought that the hypertension was primary and it induced the changes in the vessels. In proof of this conception, it has been emphasized that the sclerosis is not confined to the kidney, but represents a universal affection of the arterioles. But this explanation is not convincing either; because the height of the blood-pressure does not correspond to the intensity of the vascular changes; because the universal arteriolar fibrosis is not as pronounced nor as constant as it has been declared to be. There are many cases with an isolated sclerosis of the small arteries of the kidney. If other organs are also affected, the process in the kidney, as a rule, is the most advanced one.

In recent times, arterial spasms have been brought in causal connection with the hypertension. There is a distinct tendency to be noted to localize these spasms in the peripheral part of the vascular system. Some authors speak of contractions of the arterioles, while others point toward the capillaries (Warfield, Muenzer).

Though these contractions may be universal, they become most significant in the kidney because of the peculiar vascularization of this organ. Based upon the microscopical findings in the kidneys in early hypertension, I would suggest that the primary renal lesion should be sought in the tufts of the glomeruli. The fatal spasms occur in these. They result in a sudden interruption of the glomerular circulation and in an increase of the pressure in the afferent arterioles. The increased pressure distends the arteriolar wall. This is the first change remaining visible after death. Later the tufts, too, show signs of the harmful irritation. Their blood content becomes irregular. The capillary walls appear to be thickened and undergo hyaline degeneration (capillary sclerosis).

The afferent arterioles are not only exposed to the rise of the pressure in their lumen, but irritating matter of endogeneous or exogenous origin will also accumulate in that part of the arterial system, and act most intensively upon its wall. As a result of this direct toxic injury to the arteries, we find in the later stages proliferation of the intima, hyaline and lipoid degeneration. The differences in the extent of the degenerative changes can be readily explained by the different quality and intensity of the injurious agent.

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PITFALLS IN THE DIAGNOSIS OF DIABETES.

BY HENRY J. JOHN, M.D.,

CLEVELAND CLINIC.

Urine Analysis in Diabetes. That urine analysis alone is not a sufficient criterion in the diagnosis of diabetes, has been emphasized in various previous publications,¹ in which it has been pointed out that the presence of sugar in the urine informs us only that the renal filter is permeable to glucose, and that moreover it does not identify the level of glucose concentration in the blood at which the kidney in any individual case becomes permeable. The presence of glycosuria merely gives us a lead—a suggestion that the investigation should be carried further in order that the primary cause of the glycosuria may be established.

Glycosuria may be caused by any of the following conditions: (1) A low renal threshold; (2) a heavy carbohydrate meal; (3) diabetes mellitus. If in any case it is found that the glycosuria is due to one of the first two of these causes, it can be disregarded. It is obviously of prime importance, therefore, to be able to identify those cases in which the glycosuria is an indication of the third condition, that is, when it is due to diabetes.

When sugar in the urine is detected by the ordinary laboratory tests, (there are traces of sugar in the urine at all times, but in such a low concentration that it is not detectable by the ordinary laboratory tests), it is due to the fact that the blood-sugar concentration has been raised above the renal threshold for that case. As long as the blood-sugar level stays above this renal threshold there

¹ Methods of Precision in Diagnosis of Diabetes, a New Instrument, *Jour. Am. Med. Assn.*, 1921, 78, 103; Differential Diagnosis of Diabetes by Means of Glucose Tolerance, *Jour. Am. Med. Assn.*, 1922, 79, 1234; Interpretation of Blood-sugar Estimations that are Near the Normal, *Jour. Lab. and Clin. Med.*, 1922, 8, 145; Diabetes and Life Insurance, *Atlantic Med. Jour.*, 1923, 26, 539; Differential Diagnosis of Diabetes, *Am. Jour. Med. Sci.*, 1922, 166, 275; One Relation of Glycosuria to Kidney Permeability, *Endocrinology*, 1923, 7, 699.

will be an active excretion of sugar into the urine; when the blood-sugar level falls below this point, the excretion will cease. It is evident that if the threshold of renal permeability were at about the same level in all normal individuals, it would be a comparatively simple matter to establish the interpretation of glycosuria in any given case. Unfortunately, however, the renal threshold varies widely in normal individuals as well as in diabetics. (Table I.)

TABLE I.—VARIATIONS IN KIDNEY PERMEABILITY.

Cases showing normal glycemia with glycosuria.		Cases showing hyperglycemia without glycosuria.	
Blood sugar, mg., per 100 cc.	Number of cases.	Blood sugar mg., per 100 cc.	Number of cases.
40- 50	1	120-130	13
50- 60	6	130-140	10
60- 70	3	140-150	9
70- 80	20	150-160	4
80- 90	14	160-170	5
90-100	17	170-180	4
100-110	22	180-190	2
110-120	13	190-200	1
120 and up	2	200-210	4
		210-220	1
		220-230	1
		230-240	2
		240-250	1
		250-300	1
		300-350	1
		350 and up	0

It is due to this fact that a patient, and often a doctor as well, is perturbed by the fact that one doctor has found glycosuria and another has not, even though both examinations may have been made on the same day. The patient who because of such a disagreement on the part of two physicians has sought further help invariably inquires, "Are such different findings possible or were both or either due to a faulty test?" "It is quite possible that both physicians were right," I usually reply, basing my judgment upon such findings as those shown in Chart I. In the case of the patient whose blood-sugar curve is shown in this chart, blood-sugar estimations and urine examinations were made hourly from 8 A.M. to 4 P.M. The patient ate a moderate breakfast at 8 o'clock and lunch at 12. The chart shows that the sugar appeared in the urine when the blood-sugar concentration was 150 mg. per 100 cc. In other words, when the blood-sugar level reached 150, there began to be an active excretion of sugar, a sort of overflow into the urine. Charts II and III show a like sequence of events in a diabetic patient; namely, each meal was followed by a rise in blood-sugar with the resultant appearance of glycosuria. We may conclude that in every individual the blood stream is flooded with sugar for a shorter or a longer period after a meal, depending on the tolerance of the individual for carbohydrates, the fasting blood-sugar level in a normal individual being reached within one to two and a half hours, in a diabetic, within

six to nine hours. As far as the blood-sugar content is concerned, therefore, the difference between a normal individual and a diabetic is that in the normal individual after each meal the blood-sugar

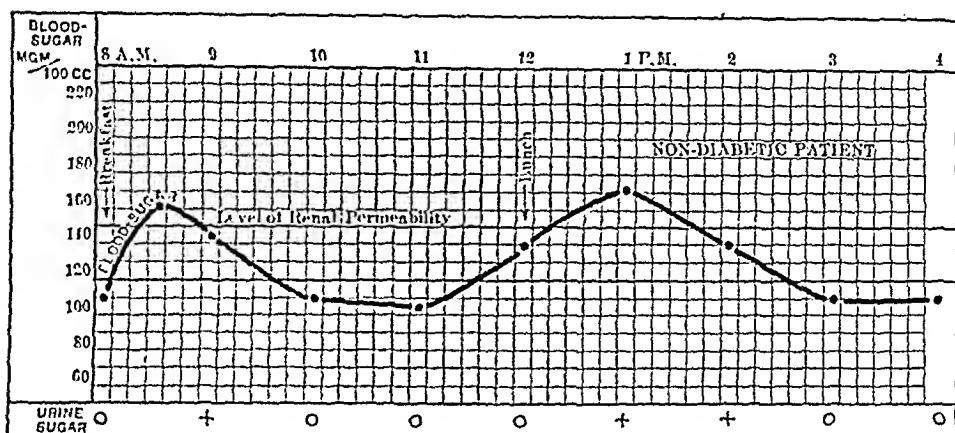


CHART I

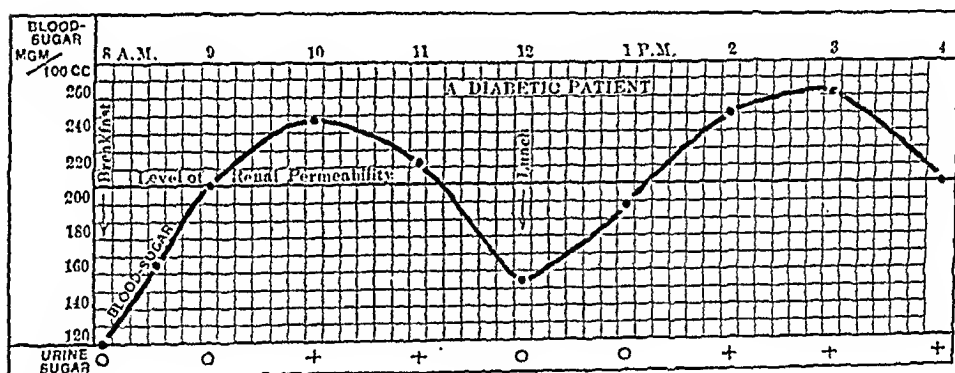


CHART II

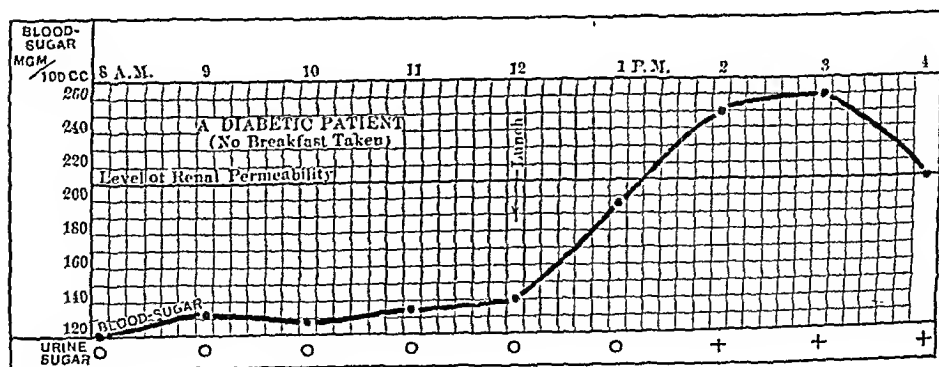


CHART III

content is somewhat increased for a short time whereas in the diabetic the blood-sugar rises to a higher level, which persists for a much longer time. Another point noted in a study of Chart I is shown by the following figures:

	A. M.				M.	P. M.			
	8	9	10	11	12	1	2	3	4
Blood sugar mg. per 100 cc.	110	146	110	106	140	172	140	110	110
Urine sugar	Neg.	Pos.	Neg.	Neg.	Neg.	Pos.	Pos.	Neg.	Neg.

It will be noted that at 9 A.M. the urine examination was positive although the blood sugar was below the permeability level. This might have been misinterpreted had we not made an examination at 8.30, a half hour after breakfast, when the blood sugar was above the permeability level. The chart shows that for thirty-five minutes the blood-sugar content was above the renal permeability level so that during this period there was an active excretion of sugar into the urine. For that reason we find glycosuria at 9 o'clock, although the actual blood-sugar figure apparently does not warrant it. A similar finding, impossible of correct interpretation by itself alone, is shown at 2 P.M. A proper interpretation of glycosuria therefore demands also a knowledge of the blood-sugar level at the time the preceding specimen was voided. If the blood sugar at that or any intervening time was above the renal threshold, glycosuria will surely be found; for the urine collected represents not only the urine secreted at the time the specimen of blood is taken, but also that secreted during a preceding period of from two to six hours. This fact explains why among the 9 urine examinations, glycosuria was found in 3 of them. It is obvious that if this individual had been examined at 10 o'clock by one physician and at 2 by another physician, there would have been conflicting opinions.

Chart II shows the blood-sugar curve of a diabetic in whom the kidney permeability level was as one would expect much higher than in the non-diabetic patient, namely, at 210 mg. per 100 cc. The morning blood-sugar was normal, as it can be in most diabetics under proper treatment. As shown in the chart synchronous examinations of blood and urine, were as follows:

	A. M.				M.	P. M.			
	8	9	10	11	12	1	2	3	4
Blood sugar mg. per 100 cc.	120	210	248	222	156	198	259	262	210
Urine sugar	Neg.	Neg.	Pos.	Pos.	Neg.	Neg.	Pos.	Pos.	Pos.

Thus among 9 urine examinations, glycosuria was found 5 times. In this case also had the patient had urine examinations made by two different physicians one at 10 o'clock and the other at 1 o'clock he would have obtained two conflicting opinions; further, as is shown by Chart III, six successive examinations on the following day, on which the patient had no breakfast would each have shown no sugar. What final conclusion could be drawn from these urine tests alone? The proper interpretation of the case is evident only when the results of the urine examinations are considered together with the blood-sugar estimations.

The above considerations of the possible variations in urine sugar content show clearly the folly of attempting to interpret a single urine finding, whether it be positive or negative.

Single blood-sugar estimation. If blood-sugar estimations are to afford any dependable information they cannot be taken at random. The result of a single blood-sugar estimation may be worse than nothing if the possibility of a postprandial hyperglycemia for example is not taken into consideration. Thus Chart I shows that at 1 o'clock in the afternoon the blood sugar was 172 mg. per 100 cc and sugar was found in the urine. Such findings might easily be interpreted as indicating a diabetic condition. Yet, in these cases as is demonstrated by the chart, nothing would be further from the truth. Again in Chart III a judgment based solely upon the low blood-sugar estimation of 128 mg. per 100 cc and the aglycosuria would lead to the conclusion that the person is not a diabetic, a dangerous judgment for the patient in view of the testimony of the whole chart.

It follows that just as a single urinary examination does not justify a diagnostic conclusion, so also a single blood-sugar examination with a synchronous urinary examination does not justify a diagnostic conclusion.

Fasting blood sugar alone and blood sugar taken three hours after a heavy carbohydrate meal. A fasting blood-sugar estimation with a urine examination alone does not offer us sufficient information upon which to base a diagnosis in all cases. If the fasting blood-sugar content is high, then the patient is certainly a diabetic whether or not there is glycosuria. But if the fasting blood-sugar content is normal or near normal, whether or not glycosuria be present, we cannot, on the other hand, say that the patient is not a diabetic. If we bear in mind that with the proper diet the fasting blood-sugar content of any diabetic may be normal, then we shall hesitate to base an opinion solely on a low fasting blood-sugar estimation.

This point is illustrated by Table II which shows fasting blood-sugar estimations and urine analyses in 41 diabetic cases with blood-sugar estimations and urine analyses in each case three hours later after a heavy carbohydrate meal. Although some of these cases were mild and others severe, in only 1 case was the fasting blood-sugar more than 130 mg. per 100 cc; in 28 cases it was below 120 mg. per 100 cc. The table shows that in every case the fasting blood-sugar content was normal but at the end of the three-hour period after the ingestion of a heavy carbohydrate meal, hyperglycemia was present. In spite of this uniformity in the blood-sugar findings at the beginning of the test, some started with no glycosuria and had none at the end; others started with no glycosuria and ended with glycosuria; others started with glycosuria and ended with no glycosuria; and others started with glycosuria and ended with glycosuria. With such a variation in the urinary findings it would be hard indeed to interpret the presence or absence of diabetes from the urinary findings alone.

TABLE II.—VARIATIONS IN GLYCOSURIA-GLYCEMIA RELATIONSHIP IN DIABETICS.

DIABETICS.				Three hours after heavy carbohydrate meal.		
Fasting.						
	No.	Blood sugar, mg. per 100 cc.	Urine sugar.	Blood sugar mg. per 100 cc.	Per cent increase.	Urine sugar.
Glycosuria: Fasting, no; at 3 hrs., no	1	115	Negative	135	17	Negative.
	2	105	"	145	35	"
	3	108	"	139	29	"
	4	84	"	155	84	"
Glycosuria: Fasting, no; at 3 hrs., yes	5	117	"	297	154	Positive.
	6	104	"	193	85	"
	7	105	"	150	42	"
	8	126	"	226	71	"
	9	132	"	467	253	"
	10	124	"	454	266	"
	11	84	"	457	344	"
	12	126	"	426	238	"
	13	99	"	297	200	"
	14	129	"	405	213	"
	15	117	"	587	401	"
	16	91	"	300	229	"
	17	130	"	294	126	"
	18	95	"	138	45	"
	19	78	"	141	80	"
	20	115	"	222	93	"
	21	108	"	261	141	"
	22	109	"	206	88	"
	23	98	"	192	95	"
	24	118	"	306	159	"
25	97	"	191	96	"	
26	65	"	175	169	"	
27	95	"	185	94	"	
28	130	"	246	89	"	
29	107	"	142	32	"	
30	129	"	308	138	"	
31	98	"	142	44	"	
32	122	"	199	63	"	
33	103	"	172	66	"	
Glycosuria: Fasting, yes; at 3 hrs., no	34	109	Positive	184	68	Negative.
	35	117	Positive	199	70	Positive.
Glycosuria: Fasting, yes; at 3 hrs., yes	36	130	"	214	64	"
	37	122	"	164	34	"
	38	120	"	178	48	"
	39	126	"	460	265	"
	40	70	"	380	442	"
	41	117	"	189	61	"

In the first group the lack of glycosuria at the end of the three-hour period means simply that the blood-sugar content did not rise at any time between the first and the second examinations.

The presence of glycosuria in the last examination of the second group of cases is readily understood as the blood-sugar content in each at the end of the period reaches above the renal threshold.

The single case in the third group requires a special examination to discover the reason for the apparently paradoxical finding. To start with a blood sugar of 109 mg. per 100 cc with glycosuria, and to end with a blood sugar of 184 mg. per 100 cc with no glycosuria, would seem at first glance, to be an error. An examination

of the successive blood-sugar estimations will explain the apparent anomaly:

	Fasting.		1 hour later.	2 hours later.	3 hours later.	4 hours later.
Blood sugar, mg. per 100 cc	109	Heavy carbo-hydrate meal.	309	348	184	122
Urine sugar	Pos.		Pos.	Pos.	Neg.	Neg.

There is glycosuria at 309, also at 348. The urine quantity at the one-hour period was very small, only 35 cc, and consequently it must have been very concentrated, so that even a small quantity of sugar could be detected by the ordinary test. There is no glycosuria at 184; this sample was larger in quantity, however (450 cc), so that a small quantity of sugar would be so diluted that it might escape recognition by the ordinary tests, even though it would be recognized in a concentrated urine. At the four-hour period the urine is still negative at 122; yet at the start it was positive with a blood-sugar level of only 109. How can we account for this?

Only one explanation seems possible, and that is the possibility of a high postprandial blood-sugar following the evening meal. If, as in this case, this figure was somewhere near 348, there would follow a gradual drop from 348 to 109 but the concentrated morning specimen would still contain the sugar from the high level, for urine always tells the whole blood-sugar story from the time of the last voiding. This would explain the glycosuria at the fasting blood-sugar level of 109 and its absence at 184 mg. per 100 cc.

The fourth group presents the obvious picture of severe diabetes, a clear cut picture of high hyperglycemia with resultant glycosuria.

These cases show what varied combinations of hyper- and hypoglycemia with aglycosuria and glycosuria are possible. The explanation of each combination is not difficult when all the data are at hand, but it is often impossible without the complete picture.

Blood-sugar examinations by the micro method. Clinicians depend for their information upon their laboratory technicians. A technician who is well trained should be able to do equally good work with different methods. Two years ago, I tried such an experiment in an attempt to see how closely a micro method would check with the macro method. The disappointing results have been published in a previous publication.¹ Since other methods used by the same technician have checked closely it appeared that the variations in the measurements by the micro method were not due to a faulty technician but rather to the method itself, which requires such small quantities of blood and of reagents in general that more than the ordinary technical ability is required in its use. Because of the inconstant results I have abandoned the use of this method.

That our experience with the chances of error with the micro method is not isolated is suggested by the history of a patient who came to us from another state where she had been treated for dia-

¹ Glucose Tolerance and Its Value in Diagnosis, Jour. Met. Res., 1922, 1, 497.

betes on the basis of a continuous high blood-sugar content. She was on a restricted diet and under insulin treatment. The day after her arrival, no insulin having been given, she showed no hyperglycemia and hyperglycemia did not appear even after a liberal diet. Moreover, the glucose tolerance test showed a normal curve. As it is obvious that severe diabetes cannot disappear in forty-eight hours, I traced the possibility of some error having been made and found that previous sugar estimations had been made by the Epstein method, the findings of which had not been checked by any other method. A repeated examination checked our findings which fortunately for the patient were found to be correct. The clinician is bound to be misled in such an instance if he is not on his guard, and we believe in view of our experience that the glucose tolerance test gives the most dependable evidence.

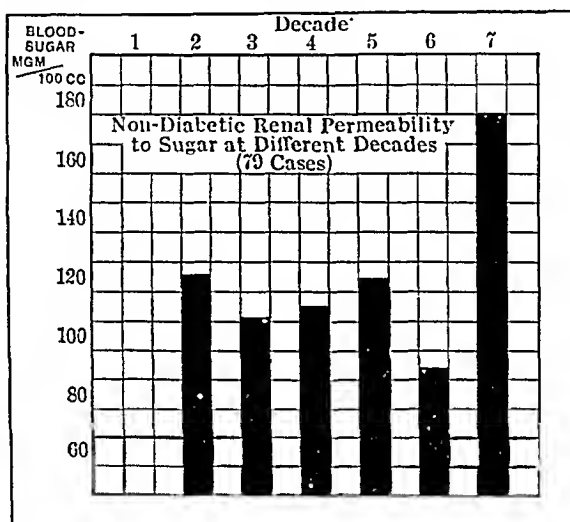


CHART IV

Charts IV and V illustrate graphically the differences in renal permeability at the different decades of life in diabetic and non-diabetic cases. With the exception of the second decade, the rise in the permeability level is slight and fairly constant. I cannot explain the abrupt and decided rise during the second decade except on the basis of the sudden onset of diabetes which is characteristic at this age. Perhaps a high blood-sugar figure accompanies this sudden development of the disease and changes temporarily the kidney permeability level.

Chart VI gives the average diabetic and non-diabetic renal permeability thresholds in 166 cases, showing the markedly higher level found in diabetic patients.

Summary and Conclusion. The finding of glycosuria alone is not a sufficient basis for the diagnosis of diabetes. If glycosuria is innocent then it is due to a low renal threshold or to an overflow of glucose as the result of a very heavy carbohydrate meal. On the other hand, if glycosuria is due to diabetes it is not innocent and there-

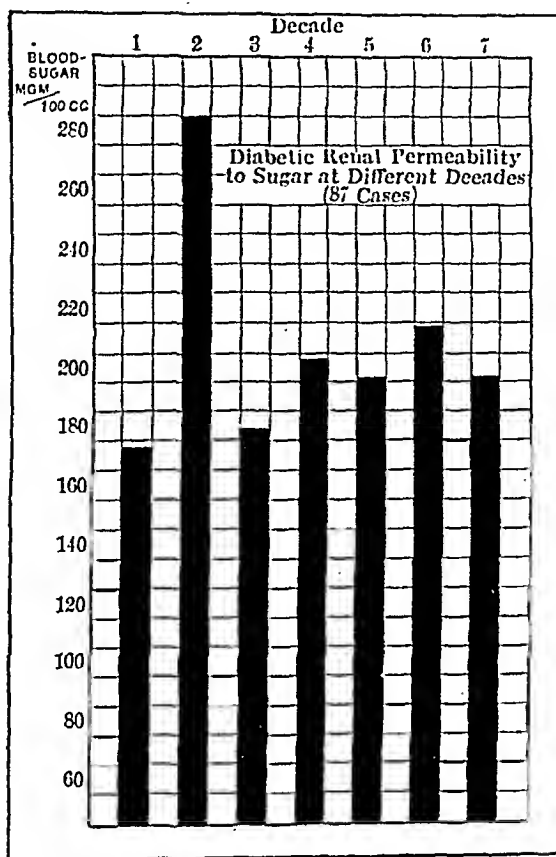


CHART V

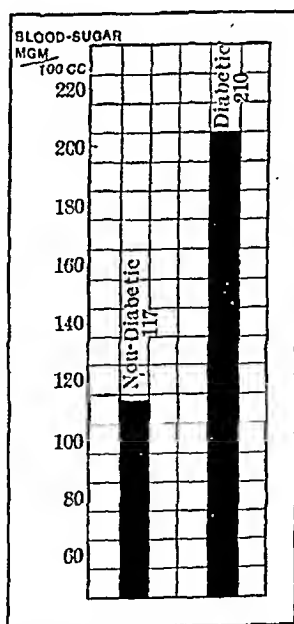


CHART VI.—The average renal permeability level in 166 non-diabetic and diabetic cases.

fore the presence of glycosuria should be considered an indication for the institution of such procedures as will determine its cause in the individual case. All that is required in such a case is to instruct the patient to eat a heavy carbohydrate meal and to present himself at the office *exactly* three hours thereafter for a blood-sugar estimation and urine examination. If the individual is normal, there will be no hyperglycemia because, in a normal individual whose tolerance for carbohydrates is unimpaired, the blood-sugar content will be normal or subnormal. On the other hand if at the end of the three-hour postprandial period the blood sugar is above the normal level, the patient is definitely a diabetic whether or not there be sugar in the urine. Thus, for diagnostic purposes, the three-hour postprandial blood-sugar estimation is of much more importance than the fasting blood-sugar estimation.

The length of time since the last meal should always be considered when blood is taken for a general estimation since the blood-sugar content varies during the day and a postprandial rise may be misinterpreted as a result. In the continued study of a case it is essential that the blood be taken always at the same periods with reference to meals, the test always beginning with a fasting blood-sugar estimation.

As has already been emphasized a fasting blood-sugar estimation alone is not of diagnostic value, since in even a severe case of diabetes the blood sugar content may be normal if the patient is on a proper diet. Due to this very fact some of our own cases have been misinterpreted in other laboratories, where, since the fasting blood sugar was found to be normal and glycosuria not present, the patients were told that they did not have diabetes. As a result these patients returned a few months later in such an advanced stage of diabetes that the administration of insulin was required. As the result of an error of this nature, a comparatively mild case of diabetes may become a severe case.

Microtechnic may lead one astray, and we believe that in general practice the glucose tolerance test gives more dependable and consistent results.

THE RELATION OF TETHELIN TO PITUITRIN.

WITH A STUDY OF TWO CASES OF DIABETES INSIPIDUS.

BY LOUIS BERMAN,

ASSOCIATE IN BIOLOGICAL CHEMISTRY, SCHOOL OF MEDICINE, COLUMBIA UNIVERSITY,
NEW YORK CITY.

IN 1916 T. Brailsford Robertson reported the isolation of a chemical compound from the extracts of the anterior lobe of the

pituitary gland. This substance, he named Tethelin. He then proceeded to study its effects upon the growth of white mice and to compare the effects obtained with those he had found when he had studied the effects of anterior lobe substance unmodified by chemical treatment. His final conclusion was that "the effects of tethelin upon the growth of white mice resemble in every particular the effects of the administration of the whole anterior lobe." He therefore considered himself justified in regarding tethelin as the active growth-promoting principle of the anterior lobe of the pituitary. Other studies made by Robertson and his co-workers showed that tethelin possessed a growth-promoting property for carcinomata in rats, in hastening tissue regeneration after inanition atrophy and in granulating wounds. In fact, a commercial preparation of tethelin was put upon the market, to be used in the treatment of indolent ulcers and burns. Barney² and Mayo³ reported good results from its use in such cases.

The physical and chemical properties of tethelin were studied by Robertson and by Schmidt and May.⁴ Upon the bases of his chemical analyses, Robertson declared that the substance belonged to the group of phospholipins but possessed the singular property for a phospholipins of being soluble in water, as well as in certain mixtures of ether and alcohol. It is also soluble in *boiling absolute alcohol*, as this is the medium which is used in separating it from the whole anterior lobe. It is important to bear this property in mind. Upon hydrolysis it yields inositol, and it contains nitrogen and phosphorus in the ratio of 4 to 1. It can be saponified, with a saponification value of about 87 mg. of KOH per gram and it has a mean iodine absorption value of 33.2 per cent. It can form 5 per cent aqueous solutions, appearing turbid brown at this concentration, but a 1 per cent solution is only slightly opalescent. Its aqueous solution does not give a biuret reaction, nor does it reduce Fehling's solution either before or after hydrolysis with barium hydroxide or with the latter followed by sulphuric acid. Ehrlich's reaction is positive, indicating the presence of an acetylated oxy-amino group, and Wiedel's reaction is positive, indicating the probable presence of an iminazoly radical. We shall return to the question of the significance of this radical for certain physiological effects of tethelin.

The work of E. P. Smith has also thrown light upon the growth-promoting activities of the anterior lobe of the pituitary and upon the physicochemical properties of the active principles. In a series of investigations, curiously enough begun in 1916, and summed up in his monograph on "The Pigmentary, Growth and Endocrine Disturbance Induced in the Anuran Tadpole by the Early Ablation of the Pars Basalis of the Hypophysis," he showed that by the removal of the anlage of the anterior lobe in the anuran tadpole, a cessation of differentiation as well as growth was produced, but

that this effect could be prevented or controlled by feeding whole anterior lobe. He also showed that the active principle concerned in this effect was *not* soluble in boiling water or *boiling alcohol*. These results of Smith in finding a growth-promoting substance in the anterior lobe which is not soluble in boiling absolute alcohol collide directly with the work of Robertson on the properties of tethelin which is soluble in boiling absolute alcohol. It follows either that the active principles of the anterior lobe of the pituitary in the anuran tadpole is entirely different from that of the white rat, which is highly improbable, for in the case of the feeding experiments of Smith, mammalian material was used, or that there are two different growth-promoting principles in the same lobe, which is also highly improbable. The possibility arises that the growth-affecting properties of tethelin, which are by no means as conspicuous as those observed by Smith using whole anterior lobe in the tadpole, may be the collateral effects of a substance having indeed another function.

This possible function has been suggested by certain physiological effects obtained when tethelin is chemically modified. In 1917, Schmidt and May¹ published a paper on the possible derivation of the active principles of the posterior lobe of the pituitary body from the tethelin produced by the anterior lobe. They based their suggestion upon the fact that tethelin when treated with barium hydroxide yielded a substance exerting on the uterus and on the blood-pressure an action similar to that of posterior pituitary extracts, usually called pituitrin. In view of the untenability of the conception of tethelin as the growth-promoting principle of the anterior lobe, as shown by the solubility findings of Smith, this suggestion remains the only one providing a possible function for tethelin (which is certainly a unique substance obtainable only from the anterior lobe) namely as a precursor of pituitrin.

In 1919, Abel and Kubata⁵ isolated from posterior lobe extracts, commonly called pituitrin, the substance B-iminazolethylamin which they called histamin because of its chemical relation to histidin, an amino-acid which may be found in the hydrolysates of various proteins. They showed that histamin is present in all the tissues of the body, and at first put forward the claim that it is the smooth muscle-contracting substance of posterior lobe extracts. They based their claim upon the fact that histamin causes an uterine reaction similar to that of pituitrin. This observation was first made by Roth and confirmed by Nieulescu. Guggenheim, however, had pointed out a difference in stability of histamin and pituitrin toward alkali in the same year that Roth pointed out the similarity of their action. Dudley,⁶ in 1919, confirmed this finding of Guggenheim, demonstrating that upon contact with sodium hydroxide, pituitrin like adrenalin loses its power to cause specific reactions while histamin is not so affected. Also that tryptic

digestion destroyed pituitrin but not histamin, and that definite solubility differences in chloroform and butyl alcohol were marked. In 1920 Hanke and Koessler⁷ showed by a colorimetric method that histamin was not present in perfectly fresh beef pituitary. In 1922, Abel and Rouiller published their observations on the preparation of a single specific substance from the infundibulum, which has both oxytocic and vasomotor properties as well as a powerful stimulating effect upon the kidney and estimated that in equal concentrations pituitrin would be found to have fifty times the uterus-contracting power of histamin. Their observations dispose finally of the claim that pituitrin and histamin are identical.

Yet the problem of the relation of tethelin to pituitrin and to histamin remains. As mentioned, the tethelin gives reactions showing presence of an iminazoly radical, which is also present in histamin. On the other hand hydrolysates of tethelin prepared with barium hydroxide give pituitrin-like oxytocic and vasomotor effects. It has been recognized that the specific test for pituitrin is its ability to reduce diuresis in the disease diabetes insipidus. It occurred to the writer to test the action of barium hydroxide hydrolysates of tethelin upon the blood-pressure and upon the diuresis of two patients with diabetes insipidus whom he had under observation, one a boy of ten and the other a man of forty-five. Both the patients had shown satisfactory response to pituitrin as far as their diuresis and general comfort was concerned.

CASE I.—Boy, aged ten years, of Hebraic descent. The father is a blonde, large individual, with a tendency to obesity but active; the mother is dark, obese and undersized. There is no history of familial diseases, but individuals in both paternal and maternal families tend to run to extremes, either large and tall or smaller than the average. The patient, an only child, was born at term and said to weigh 9 pounds at birth. He was in every way a large baby, the mother said. He was kept on the breast until three months of age, but developed vomiting which finally caused transfer to artificial feeding. Much difficulty was encountered in trying various mixtures which he could not assimilate, until one was found at the age of six months upon which he thrived, the teeth appearing at the same time. He gained quickly, perhaps as a result of over-feeding, for he weighed 33 pounds at one year. He did not gain so much during the second year, but kept over the average. At seven he weighed 54 pounds and first went to school, where he was said to be quite bright, particularly in mathematics. At eight, he had scarlet fever severely, and was in bed ten weeks, with reported development of a cardiac lesion which later cleared up. After a few months he began to complain of weakness, headache, trouble in using eyes, and great thirst. Frequent urination, nocturnal and diurnal, with thirst. He drank now about 7 to 8 quarts of water a day and passed about the same.

The physical examination showed a rather emaciated-looking boy, weighing 49 pounds and 3 feet 11 inches tall. He had a pale, sallow complexion. He was found weak, lying in bed and responding to questions reluctantly and feebly. His general build had the striking slenderness and suggestion of bony fragility that reminded one strongly of the somatic type present in the Lorraine variety of pituitary infantilism. The head was long, high and narrow; the hair of the head was light and very fine, that of the eyebrows was so light as to be almost invisible, and the outer half was practically missing. The nose was thin and high-bridged. The interpupillary space was $2\frac{3}{8}$ inches and the eyes had a somewhat mongoloid slant. The ears were oval in shape and there was very slight development of the free lobe. The teeth were large and rather trapezoid in shape and markedly separated. The palate was high and narrow, arched like a Gothic arch. The tonsils were present and just visible. The neck was relatively long in relation to the size of the head and trunk, and the thyroid gland was enlarged. Over it a soft, low systolic bruit could be heard. The heart and lungs were negative, the liver and spleen could not be felt. The hands were oblong in shape, and the lunulæ of the fingernails were all quite marked. There was no leuconychia; no Chvostek sign. The skin was fine, moist and quite light, with a few pigment spots on the neck and forearms. On stroking the skin of the chest gently, broad red lines appeared which lasted some time. The body measurements were: Torso: Lower extremity ratio, $15\frac{1}{2}$ inches to $27\frac{1}{2}$ inches; quotient, 1.8; span, 45 inches; chest circumference, $25\frac{1}{2}$ inches; sitting height, 29 inches. Examination of the blood: Hemoglobin (Sahli modified), 90 per cent; leukocytes, 8600 per c.m.; polymorphonuclears, 42 per cent; lymphocytes, 54 per cent; eosinophiles, 4 per cent. The Wassermann test was negative. Blood sugar, 65 mg. per 100 cc; cholesterol, 155 mg. per 100 cc; CO₂ combining-power of plasma, 55 volumes per cent; calcium, 9.6 mg.; inorganic phosphate, 2.7; chlorides, 760 mg. per 100 cc. Urinalysis showed: Reaction acid; specific gravity, 1001; color like that of distilled water; negative for albumin, sugar acetone and indol. Microscopical examination, negative. Eye examination: Slight bilateral concentric contraction of the visual fields and a marked contraction of the color fields, greatest on the temporal sides. Roentgen-ray examinations: Of the head showed a small completely enclosed sella turcica, while that of the chest showed a large shadow in the mediastinal region, presumably the thymus.

The blood-pressure, taken several times, averaged 95/60. The quantity of urine observed over a period of a week, averaged between 7000 to 8000 cc.

It was then decided to observe the effect of pituitrin upon the blood-pressure and the urinary output. The effect upon the urine was to reduce it to 1800 cc for the following twenty-four hours.

Upon the blood-pressure, the effects were as follows: After fifteen minutes, 100/60; after thirty minutes, 125/80; after 45 minutes, 135/80; after sixty minutes, 145/90; after one hundred and twenty minutes, 130/90; after three hours, 120/80; after 4 hours, 95/60.

There was marked subjective improvement during the twenty-four hours, the color of the face and the general vivacity increasing greatly as well as the appetite. Also a bowel movement occurred without resort to cathartics. On the day after, nothing was given and the quantity of urine rose to 6500 cc. The day after was chosen as the one on which to give the barium hydroxide hydrolysate of tethelin; 1 cc was given hypodermically. There was no effect upon the output of urine. Upon the pressure, the effect was as follows: After fifteen minutes, 100/65; after thirty minutes, 120/70; after forty-five minutes, 130/70; after sixty minutes, 135/85; after one hundred and twenty minutes, 130/70; after three hours, 110/65.

These determinations were repeated upon alternate days, with pituitrin and with tethelin hydrolysate, with the same results. It appeared therefore that while pituitrin had definite effects upon both the urinary output and the blood-pressure, the substance produced by the barium hydroxide treatment of tethelin affected only the blood-pressure. It follows that pituitrin is not present in the hydrolysate of tethelin, and that the possibility that tethelin may be the physiological precursor of pituitrin cannot be sustained. This conclusion was confirmed by observations made upon a second patient with diabetes insipidus, an adult who was seen some six months later, the details of which I shall now present. The first patient was kept comfortable with injections of pituitrin given on alternate days, and small doses of whole gland pituitary substance. But he died about a year and a half later of pneumonia, following an upper respiratory tract infection.

CASE II.—E. R., a rabbi, aged forty-five years, married, with six children, all of whom are living, about a year and a half ago began to urinate large amounts frequently. He is now passing from 10 to 20 quarts daily. At the same time he has put on over 50 pounds in weight. He was born in a small town in Russia. The family history was negative except that an uncle and a grandfather had suffered from diabetes mellitus. The past history showed that he had had scarlet fever at the age of seven and mumps at the age of thirteen. The mumps had apparently not been complicated by orchitis. The intellectual development had begun early, while the sexual development had begun late, hair on the face not appearing until the age of sixteen. He was admitted to the rabbinate at the age of twenty-three and had held the position of rabbi in his community until five years ago when war conditions forced him to emigrate to America. Here he had supported himself by teaching Hebrew, but had never obtained the rabbinate of a synagogue.

There had been much worry over economic considerations. He had married at twenty-five.

About a year and a half ago began to experience abnormal thirst. He found himself drinking every hour, then almost all the time, with a feeling of insatiable thirst. He began to pass large quantities of urine at the same time, frequently, and also began to put on weight. A desire for sweets had always been a personality characteristic; but now this desire for sweets also increased greatly and there were times when he would eat a pound to a pound and a half of chocolate a day. But this had no relation to the thirst or frequent urination, because these would continue on days when he would prevent himself from indulging in sweets.

The physical examination showed a rather large, robust man who outwardly did not appear at all ill. He weighed 187 pounds and was 5 feet 7 inches in height. His span, however, was 5 feet 9 inches. His torso measured 17 inches, while the lower extremity was $36\frac{1}{2}$ inches. His head was rather large for the height, and brachycephalic. The effect of the facial contour was rounded with prominent cheek bones. The interpupillary space was $2\frac{3}{4}$ inches, while the intermalar space was $5\frac{1}{4}$ inches. The nose was short and pointed. The ears were large, with a horizontal upper border, and the lobe running into the face. The chin was covered by a profuse growth of a black beard. The teeth were in very poor condition showing much decay and caries, with several of the molars missing. The upper central incisors were large and separated and showed large areas of erosion. The lateral incisors were small and pointed and showed several chalky white spots. The canines were not pointed. The palate was markedly arched and the tonsils were present, but did not appear diseased. The thyroid was palpable but not enlarged. The heart, lungs and abdomen were negative. The skin was smooth and soft except on the outer part of the fibiæ where it was rather hyperkeratotic. The hair of the scalp was thick, black and gray. The eyebrows were well-developed and there was a nasal brow. The axillary and pubic hairs were well developed, but there was very little hair on the extremities. The general contour of the body showed an excessive deposit of fat in the breast regions, above the pubis and over the hips and thighs and below the nape of the neck giving the body a feminine appearance. The hands were distinctly spade-like in appearance, the fingers were straight and flat, the nails showed a number of white horizontal lines. Neurological examination: Slight positive Chvostek sign. Examination of the blood: Hemoglobin (Sahli modified), 85 per cent; erythrocytes, 4,500,000 per c.mm.; leukocytes, 5600 per c.mm.; polymorphonuclears, 56 per cent; lymphocytes, 42 per cent; eosinophiles, 2 per cent. The Wassermann reaction was negative. The blood sugar was 0.78 mg. per 100 cc; cholesterol, 175 mg. per 100 cc; CO₂ combining-power of the plasma, 50 per cent; calcium, 8.7 mg.;

inorganic phosphate, 3.5 mg.; chlorides, 820 mg. per 100 cc. Urinalysis showed: Reaction acid; specific gravity, 1005; color like that of distilled water; no albumin, sugar, acetone or indol. Microscopically, a few leukocytes and cylindroids. Eye examination: Marked temporal pallor of the discs and irregular contraction of the visual fields, with concentric contraction of the color fields. Roentgen-ray examinations: Showed an enlarged sella turcica with marked erosion of the anterior and posterior clinoids and of the dorsum. That of the chest showed no pathological shadow in the mediastinal region; that of the hands showed complete closure of the epiphyses and rather marked tufting of the terminal phalanges and decreased density of the compact zone of the terminal phalanges and decreased density of the compact zone of the bones. The blood-pressure, taken daily for a week, averaged 110/70. The urine over the same period varied between 8000 and 11,000 cc. The effect of pituitrin upon the blood-pressure and urinary output was then determined. One cubic centimeter was injected intramuscularly.

The effect upon the blood-pressure was as follows:

After fifteen minutes, 115/70; after thirty minutes, 135/85; after forty-five minutes, 145/85; after sixty minutes, 150/90; after one hundred and twenty minutes, 135/80; after three hours, 120/80; after four hours, 110/80. The urinary output for the next twenty-four hours was 2460 cc, and its specific gravity rose from 1006 to 1012. The patient declared that he felt strong enough to get out of bed. His appetite was markedly improved, while the craving for sweets was greatly diminished. On the following day, however, he complained of weakness and the urinary output was 8900 cc. He expressed a continuous desire for sweets. Three days later he was given an injection of the barium hydroxide hydrolysate of tethelin. There was no effect upon the output of urine, which was 9600 cc. Upon the blood-pressure however, there was a definite effect.

After fifteen minutes, 110/70; after thirty minutes, 130/75; after forty-five minutes, 140/80; after sixty minutes, 155/90; after one hundred and twenty minutes, 150/85; after three hours, 130/80; after four hours, 115/85.

Conclusions. It is evident that while the injection of pituitrin in both cases of diabetes insipidus produced a definite effect upon both the blood-pressure and the urinary output, the barium hydroxide hydrolysate of tethelin produced a pressor effect only upon the blood-pressure, but not upon the urinary output. This seems to prove the lack of identity between the active principle present in the solution known as pituitrin and the pressor substance produced from tethelin by barium hydroxide hydrolysate. This would appear to make invalid the hypothesis which has been advanced to explain the presence of tethelin in the anterior lobe of the pituitary gland, namely, that it is produced in that lobe to act as the chemical pre-

cursor of pituitrin, which could then be looked upon as a derivation of tethelin. The pressor reactions obtained after manipulation of tethelin may be due to a freeing of the imino-azoly radical indicated by Wiedel's reaction. This may also account for statements concerning the presence of histamin in old preparations of pituitary. The function of tethelin, if it is a physiologically occurring substance and not a by-product of the chemical manipulation of the dead glandular material, therefore remains a mystery.

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GASTROINTESTINAL ULCERATION FOLLOWING CUTANEOUS BURNS. WITH REPORT OF CASE.

BY EDWARD NOVAK, A.B., M.D.,

BALTIMORE, MD.

Historical. Ulceration of the gastrointestinal tract following external burns is a subject that has attracted attention at intervals ever since 1842. In that year Curling¹ made his report of 12 cases of external burn with subsequent lesions in the intestine. Ulceration was proved at autopsy in nearly all of these cases, by the occurrence of perforation or hemorrhage in 2 or 3 others. In 2 cases inflammation only was found. In all of these cases, the lesions found were in the duodenum within an inch of the pylorus.

Curling's name has been associated ever since with duodenal ulcers subsequent to external burns. Most text-books barely mention the subject: (1) Because of its uncommonness and the lack of precise knowledge and (2) on account of the slight diagnostic and therapeutic interest.

Curling himself rather discounted the earlier observations of Dupuytren on the ground that the inflammation and ulceration described by the latter were not limited to the duodenum. Curling undoubtedly gave the first connected specialized description; but

on the question of priority the reader may formulate his own opinion from the following facts:

Dupuytren² in 1832 clearly recorded the finding of gastrointestinal inflammation and ulceration after burns. He does not delimit the areas involved—it is probable that the lesions occurred in various parts of the stomach and intestine. Specifically, he speaks of the whole ileum being bright red; of fluid blood being present in the stomach and in the intestines; of the third case he says: "In the stomach and near the pylorus there are numerous small and nearly miliary ulcerations. The whole ileum is deep red." Curling's reflection on the earlier observations implies that he considered the duodenal localization specific. This is certainly an unjustified assumption; other cases have been described in which the stomach was the site of ulcers; the present paper will record such a case.

MacCallum³ says, in connection with the subject of burns: "The duodenal ulcers so often mentioned are really rare." The textbook allusions are correspondingly timid; the only real descriptions given are in special articles.

Descriptive. Clinically the occurrence of ulceration may be heralded by hematemesis, melena or the signs of intestinal perforation. These events may take place at any time from four days to several weeks after the external burns have been sustained. One of Dupuytren's patients died in thirty-six hours and ulcers of the stomach were found. Curling's patients that showed definite ulceration at autopsy died from six to twenty-one days after being burned. In one case where the patient died on the fourth day only an inflammatory process was found in the duodenum. Perforation occurred in one case as early as the sixth day.

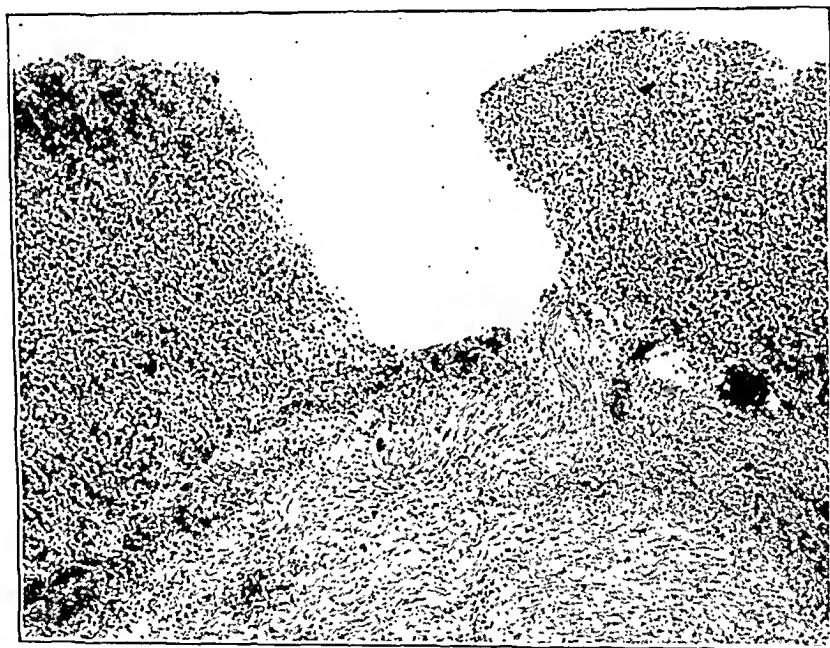
Rokitansky, as quoted by Swain,⁴ says that duodenal ulcer may be fatal in from four to sixty days after the burns are received. Simpson⁵ describes acute abdominal symptoms, suggestive of intestinal ulceration, coming on with fever more than one hundred days after the occurrence of extensive burns. This patient, however, recovered.

Not all cases of intestinal ulceration after burns have a fatal ending. Curling remarks that death from other causes, some time after burn, occasionally leads to the discovery of recently healed ulcers in the duodenum.

Pathology. The external burns may be of the first degree or more severe; in area that may be very extensive, in some cases they have involved a relatively small part, *i. e.*, less than one-fifth of the body surface.

Accurate description of the ulcers is not usually attempted in the literature. They may be miliary in size, the largest are an inch or more in diameter. A sharp edge and a clean base, perhaps grayish, are usually mentioned. The mucous membrane alone has

been involved in some instances, in others all the coats of the intestine have been penetrated. The depth of the ulceration probably is dependent in part on the factor of time; but this is difficult to determine because the time at which ulceration begins cannot be known. Perforation certainly has occurred by the fourth day after the burning; some ulcers never perforate, but heal. In the cases where perforation takes place as late as the eighteenth or nineteenth day, the ulcerative process may have had its inception the day before or two weeks before. Seldom is ulceration found when death takes place after a longer time than three weeks. It may be said, therefore, that the ulcers develop soon after the burn and progress rapidly to perforation, hemorrhage or healing. They do not become chronic.



Section through a milium ulcer, showing loss of mucosa, inflammatory reaction in surrounding mucosa, membrana propria and submucosa (lower power).

Dupuytren is well quoted here: "It has been demonstrated by postmortem observation, that when an individual has perished in a general conflagration, in the midst of flames, or a few moments after being rescued from them, inflammation has not had time to develop itself in the intestinal canal, but we there find marks of a violent congestion. If some days have elapsed since the accident, we find, on opening the bodies, all the distinctive marks of gastro-enteritis. Finally, if the patient has died at a still more remote period, we find in the viscera and particularly in the digestive apparatus, profound alterations. The mucous membrane presents more or less vivid red patches and more or less deep ulcerations."

The mucosa adjacent to the ulcer is not grossly changed; but

Leonard,⁶ in his case, observed microscopically that the cells near the ulcer were obscured; a layer of polymorphonuclear cells was seen covering the base.

Localization. In all of Curling's cases the ulcerations, when they were seen, were in the duodenum, near the pylorus. He rather implies, by his reference to Dupuytren, that lesions elsewhere in the alimentary canal are of a different nature. It is difficult to understand this assumption if the latter ulcers have been found under similar circumstances. Stengel,⁷ after calling attention to the definite relationship between cutaneous burns and duodenal ulceration, says that "in exceptional cases, ulcers in the stomach or the lower part of the intestinal tract have been found associated with such duodenal ulcers." One of Dupuytren's cases showed numerous small and large ulcers in the stomach, near the pylorus, while the duodenum was intact. In Leonard's patient, likewise, 24 small ulcers were present in the stomach, most of them near the pylorus, and the duodenum was normal. A third such case is reported in the present paper. These three instances are the only ones of the kind thus far found in a rather wide search through the literature.

Etiology and Mechanism. Hypotheses as to the cause of death in cases of superficial burn have not attained to the dignity of theories; and so it stands with regard to the causation of gastrointestinal ulceration.

Ulcer is not a constant sequela of burn. Fenwick⁸ states that it occurs in 6.2 per cent of all fatal burns. In Eriksen's⁹ series of 68 cases, two were known to have had duodenal ulcers.

Bardeen,¹⁰ in his studies of the visceral changes after burns, lists most of the possible theories of causes of death, without giving any of them especial preference. Most of the same theories have been invoked in explanation of the seemingly unaccountable occurrence of these ulcers in the alimentary canal as a complication of burns on the skin. Just as in the case of peptic ulcer and probably for the same reasons, any theory is difficult of proof. The principal hypotheses may be given brief mention.

It is conceivable, say some writers, that the damage to the skin, together with shock, suppresses the cutaneous secretion and that sympathetically the secretion of the intestinal mucosa is inhibited, rendering the tissues vulnerable. Curling states that in one case there were changes in Brunner's glands. This suggestion does not account for the ulcers found in Leonard's case, for instance, where the skin was not injured, but the burn consisted of a baking of the pelvic tissues, after Percy's method for the treatment of carcinoma of the cervix of the uterus.

That in the burned tissue is elaborated a toxic substance is another view. This substance may be excreted into the intestine. As the duodenum is peculiarly the site of the lesions, some color is given

to Hunter's¹¹ theory that the presumptive toxin is excreted by the liver in the bile. Some experimental work has been done to substantiate this view. Hunter injected toluylenediamin into dogs and noted ulceration of the duodenum. Fenwick after tying the common bile duct failed to produce ulcers in this way. Various attempts to reproduce ulcers by injecting extracts of burnt skin have failed, except that Busse¹² in this way induced hemorrhage and inflammation; these were not limited, however, to the duodenum but occurred also in the jejunum and stomach. Busse is authority for the statement that similar lesions in the duodenum may be found in those who have died of carbon monoxid poisoning.

Catiano¹³ concludes that a toxin reaching the intestinal wall causes a reduction in its natural alkalinity, allowing digestion of the mucosa to ensue. Cooke¹² thinks that reflexly the antiferments of the mucous cells are destroyed.

Minute emboli and reflex inhibition of the intestinal circulation are two further suggestions, resting upon no objective support.

Report of Case. A white woman, aged twenty years, was admitted to the Colonial Hospital on January 14, 1924. The story was that the patient's dress caught fire as she passed a gas stove and she was burned on both forearms, both legs from the ankles to the knees, on the left hip and about the left breast. In the past history there was nothing of importance. No gastric trouble had ever been experienced. She had had two children.

Examination showed a woman 5 feet 3 inches tall, weighing 110 pounds. Chest and abdomen negative. The burns were mostly of the second degree. Urinalysis showed a trace of albumin on January 16 and again on January 23; the urine was acid the first time, alkaline the second time. There were no casts, no blood. The burns were dressed with picric acid. The patient was nauseated and vomited frequently; no blood was noted in the vomitus. The urine was abundant at first but began to diminish after January 20. On January 22 she voided only 275 cc and after that very little, involuntarily. Vomiting continued. The patient became irrational. The temperature was elevated on the 17th and thereafter ranged from 99.5° to 103° F., usually above 100° F. No blood was ever noted in the stools. The patient became comatose and died on January 24. The clinical diagnosis was acute uremia due to external burns.

Necropsy. The subject is a young white female, rather emaciated. Numerous large second and third degree burns are present on the arms, body and legs. Rigor mortis is very slight. The peritoneal cavity is dry. The muscles and most of the tissues appear desiccated. The liver is of normal size, light brown in color and of firm consistency. On section the liver substance shows a slightly convex surface, yellowish-brown in color, with the lobular markings distinctly outlined by bloodvessels. There are small areas of yellow

mottling, indicating fatty change. The gall-bladder is normal. The spleen is normal in size and consistency, of a purplish-red color, with no excess of pulp or fibrous tissue. The Malpighian corpuscles are large and prominent. The kidneys are of average size, dark purple, with capsules stripping readily. The renal tissue is a little more bloody than normal, the cortex is about 6 mm. in thickness, with fairly distinct striations. The pyramids and columns are slightly swollen. Throughout the tissue, especially in the interpyramidal portions, there is a moderate amount of yellow streaking. Pelves, ureters and bladder are normal.

The stomach is greatly dilated, containing a cloudy liquid. The external surface is closely speckled with light gray areas, 2 or 3 mm. in diameter, which appear more translucent than the other portions. When the stomach is opened these lighter areas are seen to correspond to numerous small punched-out lesions in the mucosa and possibly deeper coats. All of them are within 3 inches of the pylorus. No visible inflammatory reaction is associated with the lesions, which are 40 to 50 in number. The pylorus, duodenum and both large and small intestines, also the appendix, are normal. Nothing abnormal is seen in the pelvic organs. The adrenal medulla is liquefied. The pancreas is large and quite hard, of an orange color. In the lungs there was some congestion and edema of the lower lobes and in the left lower lobe is a small patch of bronchopneumonia. The heart is negative. *Microscopical.* *Kidneys:* The bloodvessels are moderately engorged. There are a few small extravasations of blood between the tubules. The tubular epithelium is swollen and in many places necrotic. The glomeruli show accumulations of wandering cells. *Liver:* There are patches of necrosis, at the periphery of the lobules. There is a small amount of pigmentation. *Heart Muscle:* Normal except for small hemorrhages between some of the fibers. *Spleen:* Marked engorgement of bloodvessels; large numbers of wandering cells filled with pigment as well as much granular pigment in the tissue. *Adrenals:* Show nothing remarkable; no hypertrophy of the cortical elements. *Lungs:* Moderate edema, patches of bronchopneumonia in stage of red hepatization. *Stomach:* The ulcers do not go deeper than the submucosa. There is a moderate inflammatory reaction in the mucous membrane indicated by numbers of small round cells between the gland elements; these appear most numerous near the ulcers. The bases of the ulcers, however, do not show any layer of leukocytes such as described by Leonard. In a few places the submucosa and the muscularis contain numbers of round cells.

Summary. Ulceration of the gastrointestinal tract is an uncommon complication of extensive cutaneous burns, occurring probably in about 5 per cent of the fatal cases. Inflammation very likely is much more common. The condition was described by Dupuytren ten years before Curling made his well-known report.

The ulcers nearly always are found in the first part of the duodenum; but in a certain number of cases other parts of the alimentary tract are involved. At least three instances are recorded, including the author's case, in which the stomach alone was the site of multiple small ulcers.

The mechanism of the production of these ulcers is shrouded in mystery; but it seems most probable that excretion of toxic material into the gastrointestinal lumen takes place and that the mucous lining is injured thereby; just as lesions of the epithelium of another excretory organ, namely the kidney, are found after burns.

In the present case death supervened on the tenth day after the accident, without any gastrointestinal symptoms having been noted, except vomiting. Multiple small ulcers were found in the stomach near the pylorus, and nowhere else. Acute nephritis was also present.

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REVIEWS.

GRAY'S ANATOMY. Edited By WARREN H. LEWIS, B.S. M.D., Professor of Physiological Anatomy, Johns Hopkins University. Twenty-first edition, thoroughly revised and re-edited. Pp. 1417; 1283 illustrations. Philadelphia and New York: Lea & Febiger, 1924.

THE twenty-first edition of Gray's Anatomy brings up to date one of the most remarkable text-books that has ever been published in the English language. The first edition of this work appeared in 1858 and succeeding editions have appeared from time to time, so that the work has been kept up to date most consistently and most thoroughly. During the sixty-six years that have elapsed since the appearance of the first edition this book has been used by countless generations of medical students. The reviewer knows of no book that can look back to such a long and honored career. Such a past speaks well for the genius of Gray and for the succeeding authorities who have revised the subsequent editions. The new edition follows very closely the original plan of Gray, which on the whole has not been changed in any fundamental respect. In the present edition there have been incorporated new illustrations and some of the older ones have been replaced by new figures. In addition to that, the section on the heart musculature has been added and new material added to the section on embryology of the ductless glands. There are a comparatively few other changes and the new edition remains much as the previous ones. May this wonderful text-book have as wonderful a future as it has had a distinguished past.

M.

INTERNAL MEDICINE FOR NURSES. By CLIFFORD BAILEY FARR, M.D., Director of Laboratories, Pennsylvania Hospital, Department for Mental and Nervous Diseases; formerly Associate in Medicine, University of Pennsylvania. Fourth edition. Pp. 377; 75 illustrations. Philadelphia: Lea & Febiger, 1924.

THIS is one of the clearest, most succinct and well arranged text-books for the instruction of nurses that we know of. We have used it for some years now in the classes that are given in one of the large hospitals and it has always been found satisfactory for every need.

It is sufficiently wide in scope to give the nurses a clear idea of medicine, yet it is not so deep and involved that they become quasi medical students rather than nurses. This new edition maintains the high level of the previous editions. M.

A TEXTBOOK OF BIOLOGY. For Students in General, Medical and Technical Courses. By WILLIAM MARTIN SMALLWOOD, PH.D. (HARVARD), Professor of Comparative Anatomy in the Liberal Arts College of Syracuse University. Fifth Edition. Pp. 393; 249 engravings and 3 plates in color. Philadelphia and New York: Lea & Febiger, 1924.

WHILE it is obviously impossible to touch more than the very highest spots of biology in less than 400 small pages, nevertheless this book is far from a mere handbook for high-school students. It should broaden the horizon of students of medicine, as well as of natural history, and form pleasant, instructive reading to the graduates in these fields who still realize that they are students also. In the first seven chapters the principal fields of biology—the various systems of the animal body, cells, tissues, embryology—are illustrated by a single complex animal, the frog. The second and third parts deal with plant and lower animal forms, while the fourth discusses such biological problems as evolution, genetics and adaptation. K.

PATHOGENIC MICROÖRGANISMS. By WILLIAM HALLOCK PARK, M.D., Professor of Bacteriology and Hygiene, University and Bellevue Hospital Medical College and Director of the Bureau of Laboratories, of the Department of Health, New York City; ANNA WESSELS WILLIAMS, M.D., Assistant Director of the Bureau of Laboratories of the Department of Health and CHARLES KRUMWIEDE, M.D., Assistant Director of the Bureau of Laboratories; Associate Professor of Bacteriology and Hygiene in the University and Bellevue Hospital Medical College, New York City. Eighth Edition, Pp. 811; 211 engravings with 9 full page plates. Philadelphia and New York: Lea & Febiger, 1924.

FOR a new edition of such a well-known book, little more is necessary than to note the changes from the last edition, which are, however, considerable. The grouping and terminology of organisms conforms more closely to the recent adoptions of the Society of American Bacteriologists. The sections on immunity have been amplified and the authors' experiences in diphtheria immunization

given. Latest information on the value of certain sera and vaccines has been included, together with the new facts about measles, tularemia, scarlet, typhus and Rocky Mountain fever. The chapters on anaërobes, pyogenic cocci, paratyphoid and dysentery bacilli and the higher bacteria are practically rewritten. A forty-three-inch table summarizes details of the commoner bacteria, but repels by its size and clumsiness: Certainly it would not stand much use in its present position. One cannot but regret the careless proof-reading which permits "Promazek," "Leishmania," "Madsoun," "Tarbardillo," "De Kanif" and "Ocutt" (page 177) and so forth. Nor could I find any reference to the organism of inguinal granuloma, or to the part played by the reticulo-endothelial system in the development of immunity. K.

EPIDEMIC ENCEPHALITIS. By ARTHUR J. HALL, M.A., M.D., CAMB., F.R.C.P., LONDON, Professor of Medicine, University of Sheffield. Pp. 279; 17 plates and other illustrations. New York: William Wood & Co., 1924.

THIS book is made up for the greater part of Lumleian lectures delivered before the Royal College of Physicians of London in 1923. The book gives in great detail all the facts about epidemic encephalitis from the history of the disease to the treatment. The book goes into the subject with great thoroughness and the plates illustrating the pathology and certain stages of the disease are well done.

One of the most valuable parts of the book is the bibliography which makes up eighty-four pages and is composed of two thousand and fifty-six references. W.

INFANTILE PARALYSIS IN VERMONT, 1894-1922. A Memorial to CHARLES S. CAVERLY, M.D., Burlington, Vermont: State Department of Public Health, 1924.

THE Vermont State Department of Public Health has brought together in this volume not only the studies that were made in the poliomyelitis epidemics of 1914-15 but also the earlier contributions of Dr. Charles S. Caverly who was the first to report upon an epidemic of poliomyelitis (1894) in Vermont, in which State epidemics have occurred at intervals since this time.

The epidemic of 1914 was extensively studied by Dr. Lovett, Dr. Aycock, Dr. Amos, Dr. Taylor and others under the supervision of Dr. Simon Flexner. This work was made possible by the contributions of the Rockefeller Foundation. The material in

the present volume has appeared in part in current literature. It represents the application of research from a laboratory standpoint, utilized in a state-wide plan which was adopted for the prevention and treatment of these cases of poliomyelitis, a plan so thorough and comprehensive that it is now very generally adopted and used throughout the country. This volume is a splendid example of what can be accomplished in the study of disease by the coöperation of numerous specialists. It represents the most complete studies of poliomyelitis and the broadest that have ever been carried out in an epidemic. The work will well repay the trouble and expense that the Vermont State Board of Health has gone to in collecting and bringing together this material in order to make it available in a form suitable to the practitioner of medicine and the public health official.

M.

THE ANATOMY OF THE NERVOUS SYSTEM. By STEPHEN W. RANSON, M.D., PH.D., Professor of Anatomy in Northwestern University Medical School Chicago. Second Edition, pp. 421; 284 illustrations, some of them in colors. Philadelphia and London: W. B. Saunders Company.

THE second edition continues to be the most practical short anatomy of the nervous system in English. Special stress is laid on the "developmental and functional significance of structure." The outstanding omission of the first volume has been filled in by a description of the blood supply. One of the best chapters is the general consideration of the cranial nerves and their nuclei from functional standpoint. The chapter on clinical cases illustrating the anatomic principles is new and adds to the book. With but few additions the book is practically the same as the first edition.

W.

THE DIAGNOSIS OF NERVOUS DISEASES. By PURVES STEWART, K.C.M.G., C.B., M.D., EDIN., F.R.C.P., Sixth Edition. Pp. 648; 285 illustrations. New York: E. B. Treat & Co., London: Edward Arnold & Co., Printed in England, 1924.

PREVIOUS editions of this well-known work have been reviewed in this Journal. Stewart in his preface to this edition says that he has never claimed his work to be a text-book of Nervous Diseases but that it is rather an appendix approaching the subject from the clinical point of view and intended to be used in conjunction with other standard works. The reviewer can only state that he would much

rather have this book for reference in neurologic matters than the vast majority of books which pretend to be text-books of nervous diseases.

Instead of discussing the various diseases in the ordinary way, the book is divided into chapters which take up for example—coma, fits and other convulsive phenomena, affections of the cranial nerves, abnormalities of sensation, reflexes, psychoneuroses, cerebro-spinal fluid and other phases of neurologic conditions. To the neurologist this book is indispensable and to the general diagnostician it should be an absolute necessity for a quick and comprehensive exposition of nervous disorders. W.

ESSENTIALS OF PRESCRIPTION WRITING. By CARY EGGLESTON, M.D., Assistant Professor of Pharmacology, Cornell University Medical School. Third Edition, revised. Pp. 146. Philadelphia: W. B. Saunders Company, 1924.

THIS little book, pocket size, is packed with facts relative to the art of prescription writing. It should be a very valuable book to lie on the doctor's office desk for immediate reference. M.

A MANUAL OF DISEASES OF THE NOSE, THROAT, AND EAR. By E. B. GLEASON, M.D., LL.D., Professor of Otology, Medico-Chirurgical College Graduate School, University of Pennsylvania. Fifth Edition, thoroughly revised. Pp. 660; 212 illustrations. Philadelphia: W. B. Saunders Company, 1924.

DOCTOR GLEASON'S book is one of the standard text-books in his specialty and as such has run through repeated editions since its first appearance in 1907. The present edition well maintains the standard set by the previous ones and is in every way most commendable. M.

GESCHICHTE DER MEDIZIN. By PAUL DIEPGEN, M.D., PH.D., Professor of Medicine at Freiburg i.B. Pp. 146; 1 illustration. Berlin and Leipzig: Walter de Gruyter and Company, 1924.

THIS, the fourth volume of the History of Medicine Series, deals with the fundamental medical and biologic sciences, from the time of the founding of cellular pathology to the present. It upholds the high standard set by the preceding volumes in the rather surprising amount of information presented in a very brief space, and withal accurately. The work is a part of the "Goeschen Collection" which plans to present in a large series of similar small handy volumes what amounts to a synopsis of human scientific knowledge. K.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND.

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Pulmonary Infection with the Spirochætæ and Fusiform Bacilli of Vincent.—McNEILL (*Bull. Johns Hopkins Hosp.*, 1924, 35, 368) reports a unique case of advanced pulmonary disease, involving the upper third of each lung. On physical examination of the emaciated patient there was dulness anteriorly and posteriorly and intensification of the spoken and whispered voice over the upper lobes, and a few moist rales at the apices after coughing. Roentgen-ray examination of the chest showed soft, spotty infiltration in the upper two-thirds of both lungs. There was a leukocytosis of 18,500, with 39 per cent polymorphonuclear eosinophiles. The sputum was mucopurulent, sometimes blood-tinged and abundant. No tubercle bacilli were demonstrable. When the sputum was examined several hours after collection many varieties of bacteria were found, but no spirochætæ or fusiform bacilli. When the sputum was examined one to two hours after collection a few spirochætæ but no fusiform bacilli were seen. However, examination of the sputum immediately after it was coughed up showed large numbers of spirochætæ and fusiform bacilli, identical morphologically with those seen in Vincent's angina. Following four intravenous injections of neoarsphenamin and 100 gr. of potassium iodid daily by mouth, the patient recovered and gained 32 pounds in weight. Roentgen-ray examination of the lungs showed no infiltrate and the physical findings were normal. Nearly three months after treatment was begun there were 11,200 leukocytes with 17 per cent of eosinophiles. A few cases of bronchitis due to these organisms have been reported, and they have also been noted in cases of pulmonary gangrene and abscess. This, however, is the first reported case of pulmonary infection. The author suggests that cases of supposed

pulmonary tuberculosis, in whose sputa tubercle bacilli are not found, may be instances of this infection. The clinical history of this patient was that usually obtained in pulmonary tuberculosis.

Amœbic Bronchitis and the Frequent Presence of Live Entamœbæ in the Sputum and Urine during Acute Amœbic Dysentery.—PETZETAKIS (*Jour. Trop. Med. and Hyg.*, 1924, 27, 74) describes cases of bronchitis alone or associated with amœbic dysentery characterized by the following symptoms: Expectoration, at times bloody; headache; slight fever; vague thoracic pains, etc. He has studied 10 such cases in which no evidence of amœbic dysentery was obtained. Sputum, macroscopically, was at times glairy, again mucopurulent and sometimes streaked red with blood, resembling that of pulmonary tuberculosis and spirochetal bronchitis. Microscopically, entamœbæ, at times actively motile and filled with red blood cells, were found. They measured 15 to 35 microns. In a study of 34 cases of amœbic dysentery, the details of which have not yet been published, the author found living amœbæ in the sputum alone in 2 cases, in the urine alone in 1 and in both urine and sputum in 3 cases. Morphologically, they were identical with those seen in feces.

A Case of Urinary Amœbiasis.—WORSLEY and BATEMAN (*Jour. Trop. Med. and Hyg.*, 1924, 27, 278) report their study of a patient with symptoms suggesting renal calculus. Roentgen-ray examination was negative for stone. Urinary examination showed the presence of a few red cells and leukocytes and the precystic stage of *Entamœba histolytica*. The same microorganism was found in the feces. Treatment with emetine bismuth iodid, 3 gr. by mouth, and emetine hydrochloride, $\frac{1}{2}$ gr. hypodermically, was given daily for five days. This was discontinued. Then for the following six days the patient was given emetine hydrochlorid, 1 gr. hypodermically, daily. The symptoms were relieved, and examination of the urine one month later showed it to be normal.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Fractures of the Shaft of the Femur.—CAMPBELL and SPEED (*Surg., Gynec. and Obst.*, 1924, 39, 642) say that fractures of the shaft of the femur in children properly treated give excellent results. Callus in children is usually exuberant and non-union even in the presence of

infection or malposition is very rare. Young growing bones have the ability to correct even marked deformities. Immediate reduction and plaster cast is the ideal method of reduction in children, on account of the uniformly good results, the ease of handling and caring for the patients and the certainty that lack of coöperation on the part of the child cannot displace the fragments as often happens with the traction treatment. Simple fractures should be reduced immediately after injury. Early mobilization of joints and massage of soft tissues is of great importance in all fractures, but satisfactory reduction and union should not be endangered by too great enthusiasm in this respect. Compound fractures of the femur will heal without infection in 50 per cent of the cases. Non-union is due chiefly to malposition. Open reductions are rarely indicated in acute fractures of the femur. Autogenous bone grafts are the best method of internal fixation in connection with open reduction. Internal fixation is rarely indicated in children, even in non-unions. It is indicated in malunions in adults where reduction is difficult to maintain. It is always indicated in non-union in adults.

The Mechanism of Postoperative Hemorrhage.—WILENSKY and SAMUELS (*Ann. Surg.*, 1924, 90, 652) believe that the evidence appears strong that infection is the most important single factor, if it be not the only factor, causing secondary hemorrhage in operative and other wounds. The reported studies show that the presence of drainage apparatus causes an apparently protective thickening of the wall of the vessel, with which the drainage material is in close contact. Infective processes with resultant cell necrosis begins in the intima and spreads to the media. A rupture occurs in the intima and media with the formation of an aneurysmal sac; bleeding follows as a result of the rupture of the aneurysm. It seems that in cases of secondary hemorrhage that the important causative factors include an initial trauma of some kind, plus pressure of the tube or other drainage apparatus in an infected environment.

Exophthalmic Goiter Treated with Insulin.—LAWRENCE (*Brit. Med. Jour.*, 1924, 2, 753) state that four severe cases of Graves' disease with hyperthyroidism were treated with large doses of insulin, 60 to 100 units a day. The insulin was well borne and caused no inconvenience. Two of the cases were greatly improved, one being practically normal on discharge from hospital. In both the disease was uncomplicated and of less than a year's duration in women under thirty. It seems unlikely that their improvement was spontaneous or caused by any factor other than insulin. The two others were not essentially benefited, although one gained much in weight and felt better. They were cases of toxic adenoma of the thyroid, rather than of simple Graves' disease, occurring in women of about fifty and of over a year's duration. The idea of treating hyperthyroidism with insulin was founded on the hypothesis of an antagonism between hormones of the thyroid and the pancreas.

Cerebroventricular Study.—SURFT (*Northwestern Med.*, 1924, 23, 452) states that cerebroventricular studies must be used in intracranial lesions to avoid mistakes in diagnosis. Choke disks mean general cerebral edema, or local obstruction to ophthalmic venous outflow either local or general. Spinal-fluid pressure estimations are essential to the study and have no direct relation to the ocular findings, except through the medium of cerebrospinal fluid. The amount of cerebrospinal fluid is shown by the size of the ventricles as depicted by the air in the ventriculogram. Inflammatory lesions increase the amount without necessarily obstructing the circulation of the cerebrospinal fluid, but probably by retarding the absorption. Tumors change the size and shape of the ventricles by pressure, physical displacement or occlusion of the outlet of the fluid, but do not increase the amount except by prevention of the normal circulation of the cerebrospinal fluid. Tumors increase the intracranial pressure only when by their size and position they obstruct the venous outflow of the cranium. The reaction to this pressure is first venous obstruction, then cerebral edema followed by choked disks and lastly increased spinal-fluid pressure, by actual displacement of the ventricular and cisternal fluid. Decompression relieves the venous pressure and then the ocular edema.

Experiences in the Permanency of Radiological Cure in Cancer.—FORSSELL (*Am. Jour. Roentgenol.*, 1924, 12, 301) says that his material originates from a small special hospital of thirty-two beds, in Stockholm. The greatest strength of the system of after-examination lies in the fact that the Swedish Government pays the traveling expenses of poor patients to and from the hospital. Three groups of malignant growths have been observed long enough in large enough numbers to be valuable—cancer of the skin of the face, cancer of the lips and cancer of the uterine cervix. Majority of cases were treated with radium, while only a few cases have had roentgen-rays in addition. Roentgen-rays were employed in cases of large tumors, in treatment of glandular metastases and in postoperative treatment, as well as in deeply situated tumors. In cancer of lower lip the author observed cure lasting from five to thirteen years in 84 per cent of the cases; of 156 cases of skin cancer (superficial) recurrence has been noted in 12 per cent of cases. In infiltrative types recurrence has been observed in 33 per cent of cases. The author discusses the possibilities by repeated radium treatment of the radium recurrences. In the author's opinion radiotherapy in favorable cases, by weakening the tumor gives the normal mechanism of cure a chance of overcoming the disease.

Fibroma of the Abdominal Wall.—STEWART and MOAT (*Brit. Jour. Surg.*, 1924, 12, 355) say that fibroma of the abdominal wall is a simple fibrous tissue tumor, arising in the musculo-aponeurotic structures of the anterior abdominal wall, especially below the level of the umbilicus and tending to infiltrate the muscle in which it lies. It is met with in women who have borne children to the extent of 80 per cent of the reported cases, and it occasionally occurs in the scars of old hernial and other abdominal operation wounds. In other cases there is a history of local injury. A traumatic theory of origin seems reasonable and the

physiological trauma of labor would appear to be of special importance. These growths are slow in growth in the earlier stages, but with the advent of mucoid or myxomatous change a rapid increase in size may occur. They do not undergo metastasis nor do they endanger life, but there is no evidence that they disappear spontaneously. Treatment should be early and complete removal, with resection of a margin of healthy tissue wherever muscle, fascia or peritoneum is invaded by or is adherent to the growth. Recurrence means incomplete resection and demands a more radical operation. There is no evidence that sarcomatous metamorphosis ever occurs.

Recent Advances in the Diagnosis and Treatment of Urinary Lithiasis.—CUMING (*Jour. Urol.*, 1924, 12, 383) noted that the evolution of diagnosis and treatment has shown the increased possibilities of non-operative and of impacted ureteral stone. Nearly all recently impacted stones can be removed cystoscopically. There is definite opportunity to reestablish healthy activity of the kidneys in the presence of huge unilateral or bilateral stone, with advancing infection. Certain disadvantages are cited for pyelolithotomy which is usually preferable to nephrolithotomy. Necessity is shown for early radical treatment of anuria or intrarenal retention due to stones together with the wisdom of prolonged conservative treatment where adequate drainage persists. Renal and ureteral colic is due to distention rather than mechanical irritation of calculi and is coincident with advancing infection and renal destruction. Silent calculi frequently present the gravest clinical problems and the fewest symptoms attend the inoperable case. Pelvic drainage and lavage is of great value in bilateral stone cases, whether inoperable or prior to operation and in the postoperative case. Ureteral calculi often cause more damage to the kidney than renal calculi. Often nephrectomy is necessary as the result of an impacted lower ureteral calculus.

Early Recognition of Gastric and Duodenal Ulcer by Roentgen-ray Examination of Spontaneous Pneumoperitoneum.—VAUGHAN and BRAMS (*Surg., Gynec. and Obst.*, 1924, 39, 610) say that free gas in peritoneal cavity was found on roentgen-ray examination in 13 of 15 cases of anatomically proved acute perforation of gastric or duodenal ulcer, and is rarely seen in any other condition, which can be confused with perforated peptic ulcer. Free gas has been seen as early as two hours after the acute perforation occurs. The presence of free air in the peritoneal cavity is demonstrated by observing a clear distinctly bright zone, which shifts on change of posture of the patient. The gas bubble seeks the uppermost portion of the abdominal cavity. The sign is of great value because it makes possible an early and definite diagnosis. Other signs and symptoms should be used in determining a diagnosis. Earlier operation is made possible by this added method of examination. The earlier recognition and prompt surgical treatment will lower the mortality rate of acute perforation of gastric and duodenal ulcer.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Certain Aspects of Enuresis.—AMBERG (*Jour. Am. Med. Assn.*, 1924, 83, 1300) states that of the various drugs that have been employed in the treatment of enuresis atropin has perhaps held its place best. In experiments on cats it diminished the degree of contraction. In some cases atropin was administered subcutaneously. With one exception, some twenty minutes after the injection and lasting roughly for about fifteen minutes, the pulse-rate diminished. The children became more quiet. Sometimes the atropin exercises a certain influence on the bladder by decreasing the intensity of the contractions, and by diminishing the frequency. This influence is by no means marked. In one case the influence was very marked, yet the frequency of contractions was not diminished, but it was increased and there seemed to be a rhythm present but the contractions were not high. With each contraction there was a desire for urination, and it is very doubtful whether this desire was of lesser intensity. The effect of all medical measures, including drugs, hydrotherapeutic measures, electric treatment and epidural injections, has been ascribed to suggestion. Suggestion may play a part, but the author states that it is not the sole reason for success. It is difficult sometimes to differentiate training from suggestion. Hypnosis sometimes helps. The author has constructed a convenient portable electric apparatus, which is actuated by the wetting, but the current is immediately cut off. This avoids the danger of burning which is present in similar other apparatus.

Signs of Early Rickets.—MOORE (*Jour. Am. Med. Assn.*, 1924, 83, 1469) made a study of this condition because of the frequency that it was encountered in mild form in the Pacific Northwest. His observations were directed toward finding the signs and symptoms that would lead to earliest recognition. He found that the head and chest furnished the first skeletal evidence of the disease. Cranio-tabes was demonstrated in 60 per cent of the winter babies. The existence of this condition was most easily determined at the mastoid fontanel. Among abnormalities of the chest indicating rickets are the square, triangular and oval forms as measured at the plane of the fifth costochondral junction. Costomalacia, or softening of the sternal ends of the ribs, appears during the first four months of life and is an important clinical sign. Both genu valgum and genu varum are always preceded by abnormal lateral motility of the knee-joint, which is often the first sign of leg rickets. Knee motility can be measured approximately by hand or accurately by means of a very simple apparatus. Determining the amount of motility has proved valuable for both diagnosis and for prognosis.

Clinic for Treatment of Rickets with Mercury Vapor Quartz Lamp.—WYMAN and WEYMULLER (*Jour. Am. Med. Assn.*, 1924, 83, 1479) found that rickets was a very prevalent nutritional disorder in Boston. They feel that in such localities special clinics for the treatment of rickets should be organized. Acute rickets can be cured in an out-patient department by ultraviolet irradiation, the treatments being given three times a week, without any other antirachitic medication. Ultraviolet irradiation in combination with cod-liver oil is useful in treatment of acute rickets, and probably hastens the healing processes more than either ultraviolet rays or cod-liver oil alone. Ultraviolet irradiations three times a week prevents the development of rickets. If the progress of manufacturing fused quartz continues it may soon be possible to have quartz windows in every nursery, so that the baby can have its daily sun bath in a warm room. It may also be possible to devise an electric quartz bulb, simple to operate, harmless and inexpensive, which will give off sufficient actinic rays, with from one-half to one hour exposure a day to prevent rickets from developing. A simple lamp of this sort would be a part of the equipment of every nursery, and a daily sun bath with the lamp, when the baby could not be exposed to direct sunlight, would prevent rickets. The authors emphasize that while failure of calcium deposition in the epiphyses is an early and relatively pathognomonic sign of rickets, the fact should not be lost sight of that this failure of calcium deposition is only one of the many manifestations of the disease.

The Diagnosis of Dilatation of the Bronchi in Children by Means of the Injection of Iodinized Oil.—ARMAND-DE LILLE and GELSTON (*Am. Jour. Dis. Child.*, 1924, 28, 527) describe the technic of this procedure. They found that utterly aside from any other consideration the shadow given in the roentgenogram is of great interest. The contrast between other roentgenographical reproductions and those obtained by means of the injection of iodinized oil offers extremely valuable information, and should permit of definite conclusions. If there is the picture of multiple shadows in the neighborhood of the hilum, with an excessive bronchial ramification, the shadows being joined to the bronchi by a pedicle, the diagnosis of bronchial dilatation is justified. It may be demonstrated later that this conclusion must be modified in the cases of glandular cavities, but until now no such cases have been encountered. If the shadows are confluent, but can be separated by careful examination, the diagnosis of dilatation of the bronchus is again established. If the larger bronchial ramifications, without showing bunched localized shadows, appear noticeably enlarged one must admit a cylindrical dilatation of the bronchus. If there is present a number of shadows along the smaller bronchial ramifications, when they are compared to the normal picture, the diagnosis of a moderate degree of bronchiectasis is warranted. The authors claim that tuberculous cavities may be disregarded, as they are easily enough diagnosed by means of ordinary roentgenograms. It must be noted that cavities left by pulmonary abscesses are usually located far from the hilum and mediastinum, above the diaphragm, and are usually single. Aside from the great diagnostic interest presented by this method of intratracheal injections of iodinized oil in children, emphasis should be

placed on the fact that it is entirely innocuous and further holds out the hope of perhaps having a therapeutic effect of some considerable value. They have observed in a number of young patients a marked lessening of physical signs, indicating a diminution in the size of the bronchial cavities. It would appear that there was a local effect of the iodine. This has not been checked by second injections.

Non-rachitic Softening of the Ribs in Infants and Children.—HESS (*Am. Jour. Dis. Child.*, 1924, 28, 568) remarks that, although the usual phenomena of rickets are cured by the use of cod-liver oil or ultra-violet irradiations or both, these two procedures have no effect upon the softening of the ribs. Seasonal variation, which plays so important a part in the development and cure of rickets, was found to have no relation to the appearance or recession of this sign, no improvement at all taking place in the summer months. This condition is not amenable to treatment. A striking feature is that the softening was found almost always in infants who were or had been poorly nourished. This was not a characteristic of rickets. As is well known, rickets is frequently met with in babies who are overweight or robust. In this type of baby rickets is not associated with softening of the ribs. No association has been noted between this clinical condition and any particular sign of rickets. It was not associated more often with craniotabes than with beading of the ribs or enlarged epiphyses. The only peculiarity was that the circumference of the heads of many of these infants was large in comparison to that of their chests. This tended to give them a slightly rachitic appearance. Some infants seemed to have a slight hydrocephalus accompanied by a widening of the fontanel. The softening of the ribs and their cartilages led to a sinking of the anterior wall of the chest and to a flattening of the chest. This change in conformation was apparent in some instances on casual examination and was confirmed by measurements of the thorax. Although the circumference of the chest was normal in infants with soft ribs, the anteroposterior diameter was less in comparison to the lateral diameter than in infants with firm ribs. Some of the children had deformity of the chest, commonly called "chicken-breast," or a "funnel-shaped chest." These deformities may result from rickets, but they may likewise come about from other causes. Pneumonia may lead to "chicken-breast." The most common etiological factor of these two malformations is rickets combined with softness of the ribs.

Correlation of Clinical, Roentgenological and Serological Evidence of Rickets in the Breast-fed.—DEBUYS and VON MEYSENBURG (*Jour. Am. Med. Assn.*, 1924, 83, 1563) studied sixty-eight infants, with an analysis of clinical findings, roentgenological picture and blood chemistry. They found that the positive roentgenographical findings, the positive clinical manifestations and the abnormal blood chemistry ran parallel. A few cases in which there was marked disagreement between positive clinical findings and negative blood findings were attributed to residual rickets after the use of cod-liver oil. Epiphyseal enlargement is remarked upon as the most dependable clinical manifestation of rickets. Costal beading appears to be the next most important sign. Although craniotabes occurs regularly in those cases with a low calcium-

phosphate product, it also appears so often and in such a marked degree in cases with normal blood and roentgen-ray findings that it is unreliable if considered alone. This symptom is unreliable because of its appearance at an early age and because of its short duration. Cranial bosses, flaring ribs and bowed legs must be regarded as later changes of rickets. In the first twelve weeks of life the blood does not show any changes that are indicative of rickets. From the twelfth to the twentieth week the blood changes are more pronounced, and after this period there is a gradual return to normal. The seasonal variation of blood phosphates was noted, the lowest ebb being in March.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Acute Ulceration of the Vulva.—McDONAGH (*Brit. Jour. Dermatol.*, 1924, 36, 285) discusses the characteristics and differential diagnosis of ulcerations of the vulva due to Doederlein's bacillus (*Bacillus crassus*) and Vincent's organism. The two conditions have many points in common. In both, the local process is ushered in by constitutional disturbance, chills and fever. In neither disease is the lesion auto-inoculable, or transmissible to animals. Aphthous ulcers in the mouth coincidently with vulvar ulceration in one of his cases lead the author to question whether, from the finding of both organisms in the mouth lesions, there may not be a relation between the Doederlein organism and the Vincent fusiform bacillus. The author, widely known for his heretical views on the etiology of syphilis, proposes for consideration the fundamental relation of the two vulvar conditions named and cites as analogous examples the conditions known clinically as granuloma pudendi and *ulcus molle serpiginosum*, in which, McDonagh believes the Ducrey streptobacillus takes on an intracellular habitat and a capsular form. In discussing *ulcus acutum vulvæ*, McDonagh emphasizes the youth and frequent virginal condition of the patients; the severity of the pain, which may even cause retention of urine; the grayish-white surface of the ulcers; their localization on the inner aspects of the lesser labia; the fact that no erosion precedes the ulcer; the lack of tissue destruction as compared with Vincent's infection of the same region, and the absence of a distinctive foul odor, as important descriptive and differential points as against Vincent's ulceration. The Doederlein bacillus is Gram-positive, varies much in length but is of uniform thickness (0.5μ) and has right-angled ends. The bacilli are frequently found in short chains, and long forms may stain unevenly. Culture is possible on maltose ascitic-fluid agar, preferably under anaërobic conditions. Vincent's organism may cause an infection

de novo or a superinfection. Inguinal adenitis is common. The odor is most characteristic and highly offensive. Erosions appear first, followed by ulceration and incredibly rapid phagadenic destruction of tissue. Bathing with hydrogen peroxide and the administration of 2 or 3 injections of arsphenamin and no more, is recommended. The author states that if this number of injections is exceeded, the process may light up again and extend with renewed violence. The author believes that syphilitic patients are specially prone to develop Vincent infections.

Pigmentation of the Skin Associated with Lymphosarcoma.—The report of WARTHIN, CRANE and JACKSON (*Arch. Dermat. and Syph.*, 1924, 10, 139) is of interest to the dermatologist because of a discussion of the interrelations of the various pigmentary syndromes associated with abdominal pathology and endocrine involvement. Speaking of acanthosis nigricans, the pigmentary and papillary dystrophy of the skin associated in adults with malignant processes, in the abdomen and sometimes seen in juveniles without a malignant background, the authors emphasize the variety of clinical pictures included in the designation. Emphasis should be placed in these cases and in true Addison's disease upon atrophy of the chromaffin tissue as the etiologic background of the pigmentation. Warthin and his co-workers advance the view that pigmentation of the skin in these abdominal sympathetic syndromes is the result of the activity of reticuloendothelial cells lying in or near the walls of the capillaries of the corium, rather than of the activity of the basal layer of the epidermis. The source of cutaneous pigmentation is then, the chromatophore in the cutis, not the melanoblast in the epidermis. In the cases reported, a pigmentation of the surfaces of the lymph nodes nearest the skin leads the authors to infer that an actinic source such as roentgen-rays or light is responsible for the formation of melanin. To quote their statement "We may advance the hypothesis that, as the result of atrophy or destruction of chromaffin tissue, in the abdominal sympathetic ganglions and suprarenals, there is a disturbance in the production of the aromatic compounds of the pyrocatechin group (mother substances or precursors of suprarenalin) which, circulating in the blood, are taken up by the reticuloendothelial cells of the corium and transformed into melanin under the action of light (ultraviolet) or oxidative ferments (dioxyphenylalaninoxidase)."

Tensile Strength of Hair.—CHENG (*Arch. f. Dermat. u. Syph.*, 1924, 147, 550) finds from studies of the tensile strength of hair, that hair from which the fat has been removed is decidedly weakened and breaks more easily than hair which is oily or of normal fat content. He remarks upon the essentially unphysiologic character of many of the methods employed at present in dressing and treating the hair, in that they tend to produce a brittle, friable hair of low tensile strength.

Treatment of Chancroid.—REENSTIERNA (*Arch. f. Dermat. u. Syph.*, 1924, 147, 362) reports the results of the treatment of 153 patients with chancroidal bubo (Ducrey infection) with an antistreptobacillus

serum obtained from rams and mixed with a sufficient amount of killed typhoid organisms to produce a febrile reaction. In cases in which the bubo had not been opened for drainage with resultant secondary infection, involution was accomplished in an average period of one week (five to ten days) which was one-fourth of the period required for a series of untreated chancroidal bubos to run their course. The chancroidal lesion itself is favorably influenced by this mode of treatment, but less by the antiserum alone. Two injections are given, separated by an interval of three to five days. A chill and febrile reaction with some local reaction at the site of injection and enlargement of regional lymph nodes follows the injection of the preparation, but no significant complications have occurred. In cases requiring further treatment of the chancroidal lesion, the application of heat, to which the Ducrey organism is especially susceptible, is recommended.

Kolmer Modification of the Wassermann Test.—IRVINE and STERN (*Arch. Dermat. Syph.*, 1923, 8, 818) present a valuable report of the results of the Kolmer modification of the Wassermann test in 5162 tests checked against the standard procedure of the laboratory of the Minnesota State Board of Health and against the clinical follow-ups of the cases. In 91.5 per cent there was agreement between the two tests. Of the 249 cases in which there was disagreement, 211 yielded positive Kolmer tests and negative routine tests. In this series in which the Kolmer proved itself to be more delicate than the routine only 3 cases occurred which did not have a history and clinical symptoms of syphilis. Of 43 cases in which the Kolmer test was positive and the routine test doubtful; only 2 had no clinical symptoms of syphilis. Of 108 tests which were doubtful only 1 failed to show clinical syphilis. Of 42 in which the Kolmer test was negative and the routine positive, the clinical follow-up indicated 11 cases of pulmonary tuberculosis, 13 cases of pregnancy with no symptoms of syphilis, 4 questionable diagnosis, 3 diagnosed syphilis, 2 cases of encephalitis, 1 case of Vincent's angina, 1 of eczema and 7 in which there were no symptoms of syphilis. The same type of findings indicated the greater reliability of the Kolmer test when the routine test was doubtful. In early syphilis the routine test gave 42 definite false positives as against a possible 5 for the Kolmer test. The Kolmer test yielded positive Wassermann reactions earlier in primary syphilis than did the routine test with an acetone insoluble antigen. Serum subjected to shipment or kept for varying periods showed more reliable results by the Kolmer than by the routine procedure and the Kolmer test could be trusted until the fourth day after drawing blood. It was found incidentally that there was less danger of wrong results from stale serum in syphilitic than in non-syphilitic processes. In the study of pregnant patients it was found that the Kolmer test showed little or no tendency to false positives, and yet did not miss true positive cases. The authors conclude that the Kolmer technic has many advantages over the ordinary Wassermann procedures, the only disadvantage being the larger amount of work involved and the delayed report due to the long ice-box incubation period.

OBSTETRICS

 UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Progress in the Relief of Sterility.—CURTIS (*Am. Jour. Obst.*, July, 1924) reviews the literature on the subject and also what has been accomplished in actual clinical work. He concludes if husband and wife give histories of good health, critical examination reveals no indication that a diagnosis of relative sterility is warranted only after the observation of three years. During this time the simplest treatment only is required. In but a very small percentage of cases is general ill health or improper diet or various physiologic disturbances the cause of sterility. Gonorrheal infection and infection following abortion are the most important and the most frequent causes. It is difficult to cure gonorrhea and very difficult to know when such a cure has been effected. The frequent practice of curettage is injurious because it tends to induce infection. Patients otherwise healthy are frequently found where sterility has followed the development of infection excited by curettage. Where there is no other pathology, the cure of abnormal conditions of the cervix is often followed by pregnancy. This is especially true where there is congenital obstruction of the canal or cervicitis with a purulent discharge. In contrast to this is the clinical fact that treatment of the body of the uterus has little influence in promoting conception. Where there is sterility with tubal disease, treatment—and by operation—gives much better results than formerly. Such cases should be very carefully selected and given appropriate treatment before operation.

When is Sterilization Indicated following Cesarean Section.—SWIFT (*Jour. Am. Med. Assn.*, July 19, 1924) considers this question in the light of his experiences in the Boston Lying-In Hospital. He reviews the histories of 95 patients who had repeated Cesarean section and exclusive of the original Cesarean section, 16 of his operations were done upon these patients. Fifty-seven of these 95 had a second Cesarean section; 21 had a second and third; 11 had a second, third and fourth; 2 had a second, third, fourth and fifth and 4 had a second, third, fourth, fifth and sixth. Among these patients were 4 deaths. Taking a large number of original Cesarean operations, in 850 cases, the mortality was 5.6 per cent. These were unselected and for all possible indications. This percentage is too high and does not represent the mortality at the present time when the operation is done under proper conditions and skilfully. The risk of a repeated Cesarean section is less than that of a primary section and the writer quotes cases illustrating this point. The convalescence after repeated section is more comfortable than with the primary operation. In the cases which he studied, there was no actual rupture of the old scar. Several of the scars showed definite weakness, but none ruptured. If such a patient is under close observa-

tion and the operation is done before or just as labor is commencing, the risk of rupture of the scar after Cesarean section is exceedingly slight. The writer believes that no patient should be sterilized without the written consent of both herself and her husband after they have thoroughly understood what sterilization entails. Each case presents a separate and different problem, but no woman should be sterilized in her first Cesarean section unless there are definite indications other than the possibility of a second Cesarean section. As successive operations increase, opinion tends toward suggesting and eventually urging sterilization. The writer believes that no patient should have more than 4 Cesarean operations. Methods of preventing conception from a medical standpoint are unreliable. It must be remembered that any Cesarean section carries more risk to the mother than delivery through the natural passage, but conditions may arise in which sterilization is justifiable. In discussion Holmes stated that in cardiac disease, chronic interstitial nephritis and tuberculosis complicating pregnancy, Cesarean section, when indicated, should include sterilization. Pelvic deformity is not an indication for sterilization. Where husband and wife request sterilization at a second Cesarean section, they must consider the fact that their children then living may die and the birth of other children will be impossible. They have, however, the right to insist that sterilization be performed. The danger of rupture of the scar is considerable and all women having had 1 operation should be in the hands of competent obstetricians during the second pregnancy. The question of State control of sterilization came up in discussion and it was believed that the decision in these cases should be left with the physician.

Morphin and Magnesium Sulphate as an Obstetrical Analgesic.—ADAMS (*Am. Jour. Obst.*, September, 1924) reports his results in the obstetrical and gynecological clinic of the University of Michigan. He used a 25 per cent solution of chemically pure magnesium sulphate, this was sterilized when required by boiling, it was then drawn into a sterile hypodermic syringe and the desired amount of morphin sulphate added. The injections were made into the deltoid muscle, the cases were not selected but were done as they entered the service. Sixty patients were so treated, 6 multiparæ and 54 primiparæ, the youngest fourteen and the oldest thirty-nine years, the average age was twenty, all were at term and all started labor spontaneously. Labor was slightly shorter than the average, there was no excessive postpartum bleeding, although one patient had a deep cervical tear. The uterus did not relax. Thirty-five of these cases had an ampoule of pituitrin after the delivery of the child, these patients had a greater blood loss than those who were not so treated. No bad results followed the treatment. Eighty-five per cent of the children cried spontaneously within one minute of birth; in 13 per cent there was slight cyanosis with normal heart beat; in 2 per cent there was pallid asphyxia and one child could not be resuscitated, autopsy revealed an enlarged thymus and a blood Wassermann of 4 plus. Comparing these with other cases where this method was not used, a very slight difference in favor of this method was observed with infants. Among these patients so treated 90 per cent delivered themselves, 8 per cent were delivered by forceps and in 1 case Cesarean section was done; the forceps were used for contracted

pelvis in 2, failure of rotation in 2, large child in 1. Comparing these with other patients, the use of forceps was a little less frequent, about 1 per cent in cases receiving the morphin and magnesium sulphate. At first the dose used was $1\frac{1}{2}$ cc of 25 per cent solution of magnesium sulphate and $\frac{1}{8}$ gr. morphin. This dose was ineffectual and 2 cc of the magnesium sulphate and $\frac{1}{6}$ gr. of morphin gave better results. The dose was repeated in 13 cases, 21.5 per cent. When this medicine was given the average dilatation was $4\frac{1}{2}$ cm. So far as the results are concerned in 93.4 per cent cases patients were more or less relieved by the treatment, in 6.6 per cent no results followed, 25 per cent had extremely easy labors with practically no pain until late in the second stage when ether was used. Ether was given in the last of the second stage in practically all the cases.

Fibroids in the Puerperal State.—FISCHMANN (*Surg., Gynec. and Obst.*, September 19, 1924) reviews the literature of the subject and reports the case of a primipara, aged forty years, large and well nourished with a large and symmetrical abdomen. On palpation two ovoids could be made out and but one heart sound. A roentgen-ray examination was requested, but refused. Labor began with rupture of the membranes and was tedious, finally terminating by the extraction of a male child weighing 8 pounds, $8\frac{3}{4}$ ounces, by the low application of the forceps. The uterus remained large and there seemed to be another fetal ovoid on the right side. On removing the placenta by the hand, the right side of the uterus was found to be occupied by a semi-solid mass of unequal consistency. An hour and a half after delivery the patient had chills followed by fever which persisted for the next four weeks. The uterus remained large and there was a profuse and exceedingly foul discharge. The patient was placed in Fowler's position for drainage, ergot was given and iodine douches. About a month after delivery, following labor pains, there was a free discharge of pus with continued pain and on the following day the cervix was dilated by a mass which felt like a macerated fetal head. Under gas anesthesia this mass was finally delivered by Tarnier forceps. The uterus contracted, the fever subsided and the patient recovered. During her illness the blood cultures were sterile, the lochia showed many colon bacilli and staphylococci and there were colon bacilli in the urine. On examination the tumor was found to be fibroid more or less degenerated and necrotic and with localized suppuration. The degenerative changes were of about four or five weeks' duration. Opinions differ concerning the treatment of fibroids complicating pregnancy. The complete disappearance of the tumor after labor has been observed, but is rare. Some urge that no interference be practised unless the tumor is so situated as to render labor impossible. Others believe that operation should be performed at the beginning of labor in all cases. In the puerperal period, should symptoms of infection develop, hysterectomy should be done as soon as possible. Vaginal operations in these cases are often unsuccessful. Attention has been called to the danger of inversion of the uterus by spontaneous expulsion of a fibroid tumor after labor. In the experience of the reviewer a multiparous woman passed through a spontaneous confinement in the hands of a general practitioner without unusual symptoms. Her recovery was slow with attacks of pain and bearing-down. She visited several gynecological

clinics for relief. Several weeks after labor she was taken with pain and some discharge and her physician was summoned who found a mass on the perineum whose nature he did not recognize. He made traction upon this to deliver and succeeded in bringing it outside the vulva, when the patient had shock and great pain. He then desisted and called consultation, taking the patient at once to hospital. On examination a fibroid tumor had been expelled attached to the fundus of the uterus by a slender pedicle. Traction upon this pedicle had inverted the uterus. The tumor was readily removed and the uterus replaced, but the patient died of shock.

A Cervical Dilator for Use During Cesarean Section.—DOUGAL (*Jour. Obst. and Gynec., British Empire*, 1924, 31, No. 2) has experienced, as have many others, difficulty in dilating the cervix in elective Cesarean section for the escape of blood from the uterine cavity. Drainage should always be secured after section, for retained blood in the uterus may set up after-pains and cause shock. It is sometimes possible to dilate the cervix from above through the uterine incision by the finger and some have passed a solid dilator from above, allowing it to enter the vagina from which it was subsequently extracted. The writer has devised a gutter-shaped dilator which he passes through the cervix from the uterine cavity, forming a channel through which blood can easily flow. It is $7\frac{1}{2}$ inches long by $\frac{5}{8}$ inch in diameter, and to introduce it a retractor is placed in the lower end of the uterine incision and the internal os dilated. The dilator is then inserted and pushed down until the upper end remains in the lower uterine segment; at the close of the operation the top of the dilator usually projects about $\frac{3}{4}$ of an inch from the vaginal orifice and can readily be removed. If it has lodged upon the perineum, it can also be readily extracted.

The Test of Renal Function in the Parturient Patient.—LORENZETTI (*Ann. d. Obstet. e Ginecol.* 1924, No. 9) has studied this question and concludes that the normal kidney function is not greatly disturbed in healthy pregnant women. The quantity of urine secreted has a tendency to lessen during the latter part of pregnancy and the puerperal period. A slight albuminuria during pregnancy is not uncommon and this may increase somewhat during the first days of the puerperal period. Primigravidæ are more susceptible to this than multigravidæ. In the presence of nephritis a genuine insufficiency of kidney function naturally develops. This may or may not be accompanied by eclamptic convulsions. Where the patient has had chronic nephritis, in the event of pregnancy and parturition there may be sudden kidney failure. Where pregnancy is complicated by heart disease or tuberculosis kidney function may suddenly and unexpectedly fail during labor or immediately after. The cause for this is more in the pathological condition present than in the pregnancy. Neither polyuria nor oliguria essentially influence the actual secretion of urine. Where the phthalein test is tried, its percentage does not always correspond with the quantity of albumin present or the number of casts. In a pregnancy complicated by renal lesions it may not be possible by the phthalein test only to modify the patient's condition by treatment, but the use of this test is of service in furnishing indications for treatment and in some cases for the interruption of pregnancy.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

End-results of Surgical Treatment in Cervical Cancer.—Reporting the work from Peterson's Clinic at the University of Michigan, Cron (*Wisconsin Med. Jour.*, 1924, 23, 128) states that during the years from 1902 to 1920 there were 380 cases of cervical cancer admitted for diagnosis. They were clinically classified in two groups, either as early carcinoma when the lesion was localized to the cervix, or advanced where the involvement had extended to the vagina, bladder, rectum or outward to the parametrial regions, sacro-uterine ligaments or lymph glands. During this period of eighteen years only 60 cases were seen which could be classified as early cervical carcinoma. The remaining 320 were judged far advanced or at least inoperable from the standpoint of performing the radical Wertheim operation. During the early years zinc chlorid packs in and against the cervix was a favorite method of attack in the inoperable cases. Later excision of the cauliflower mass and curettage followed by cautery were favored, then cautery alone and finally Percy's much heralded technic of cauterization guiding the procedure by means of an assistant's hand in the abdomen. Since then the acetone treatment has been tried and more recently the roentgen-ray. Every patient excepting 1 eventually died directly or indirectly from the uterine malignancy. Of the 60 operable cases, 18 patients (40.9 per cent) are living and well five or more years after operation. When one considers, however, the end-results of all cases of cancer of the cervix seen in this series, it is found that only 5 per cent, or 19 out of 380 women, were cured. No wonder the great horror and fear women have of this disease. As a result of his study of this series the author comes to the conclusion that the life of women with advanced carcinoma of the cervix treated by packs or actual cautery is not materially lengthened, although the vaginal discharge and bleeding may be temporarily relieved. The percentage of cures in women with early carcinoma who survive the radical abdominal operation is favorable, but when one considers all the cases of cancer, the results from surgery alone are most discouraging. Deep roentgen-ray therapy by high voltage gives excellent palliative results and has replaced surgery in advanced cervical cancer; in fact radium and roentgen-ray should be used in all cervical cancer. Whether radium, roentgen-ray and surgery combined in early cancer will give better end-results than radium and roentgen-ray alone is still a disputed question which will only be decided after experience over a long period of time.

Plastic Restoration of the Tubal Canal.—There are occasional cases in which it may be advisable to restore the tubal connection to the uterus after previously having separated the tube from the uterus. STRASSMAN (*Zentralbl. f. Gynäk.*, 1924, 48, 1681) presents two cases in which such a procedure was advisable and describes his technic in detail. In the first case a dermoid cyst adherent to the tube necessitated removal of the left tube and ovary, while on the right side there was a pregnancy in the interstitial portion of the tube, and not desiring to remove the entire tube, only the interstitial portion with the uterine cornu was removed. The remaining part of the tube was sutured into the opening in the cornu in such a manner that the end of the tube hung free in the uterine cavity. The fimbriated end was not disturbed. This patient expects to be married soon and has a great desire to have children. In the second case the patient had been married eight years but never had any children and at operation it was found that she had chronic pelvic inflammatory disease. The fimbriated end of the left tube was closed and a salpingostomy was done, although the author realized that the end-results of this operation are seldom favorable. On the right side the inflammatory disease was confined to the inner portion of the tube (salpingitis isthmica nodosa), the outer portion being patulous. The isthmus of the tube was removed and the outer portion implanted into the cornu of the uterus through a 2-cm. incision. Here again the anastomosis was made so that the end of the tube hung free in the uterine cavity. The uterine wall was closed over the tube with only one suture so that there would not be too much pressure on the tubal tissue. The operation is easily performed provided care is taken to ensure complete hemostasis, and thus avoid a hematoma and breaking-down of the wound. The technic is very similar to the implantation of the ureter into the bladder. The operation is only advisable when the opposite tube is not patulous and should never be done when the other tube is normal. Furthermore, the part of the tube to be implanted must be patulous to a sound and apparently healthy. In fact, by threading the tube over a sound it is easily held in place while the anastomosis is made and the uterine wound sutured. It should also be remembered that the operation should only be done when the woman desires children and is in a proper physical condition to bear them. A case in which an operation of this type was followed by pregnancy was reported from Cullen's clinic a few years ago.

Primary Carcinoma of Urethra.—There have been only 99 authentic cases of primary carcinoma of the female urethra reported in the literature, and in adding one case to this list, O'CONOR (*Jour. Urol.*, 1924, 12, 159) describes a very extensive urethral carcinoma which was locally destroyed with subsequent complete healing of the urethral and vulvar regions by means of diathermy. Complete urinary function was retained and local symptoms were completely relieved by the procedure. He is quite enthusiastic over the result and suggests that diathermy offers a method which is superior to any previously described in effecting the local destruction of carcinoma of the female urethra. This is especially true if we bear in mind the minimization of metas-

tases by the complete sealing off of the surrounding tissues during the slow coagulation. The procedure is devoid of operative shock, a general anesthetic is unnecessary, postoperative discomfort is slight and even in advanced cases urinary control can be maintained. The treatments which have been tried heretofore for this distressing condition make us hope that diathermy will do in similar cases what it apparently has done in this particular case of the author.

Childbearing after Radiation.—PEMBERTON (*Surg., Gynec. and Obst.* 1924, 39, 207) has been questioned so many times by physicians in regard to the danger of causing poorly developed, deformed or backward children or even sterility in fertile women by the use of radium for therapeutic purposes that he believes that the known results are not common knowledge and therefore he discourses upon the subject. He reminds us that the result of radiation in the ovary is well established by the examination of animal and human ovaries after treatment. The maturing Graafian follicles are more susceptible to radiation than the primordial follicles, which is very important, as will be seen. In a well developed follicle the changes consist in a degeneration and destruction of the ovum and membrana granulosa, preventing the follicle from going on to maturity and leaving a small cyst. In less advanced follicles the ovum is destroyed but the single layer of granulosa cells is preserved. If a dose has not been large enough to cause a menopause, however, the primordial follicles remain intact, capable of maturing normally. Theoretically then, it is possible to use such a dose of radiation that mature follicles may be destroyed but primordial follicles not damaged. This is what seems to occur clinically. Following treatment the patient may menstruate normally, have a scanty flow, or amenorrhea for a few months depending on the size of the dose. If amenorrhea occurs with this small dosage it is followed by a reestablishment of menstruation except in rare unusually susceptible cases. Ovulation and menstruation are believed to be definitely related to each other. Therefore theoretically if menstruation is present, fertility is possible. The other important consideration is the possibility of the fertilization of a partially damaged ovum. Theoretically this might result in a deformed or poorly developed child or a so-called blighted ovum. There appears to be no data in regard to this point. The percentages of miscarriages is greater in radiated than in normal mothers, but no one has reported the birth of a deformed child and only a few underdeveloped ones are found. At the Free Hospital for Women, Pemberton reviewed reports obtained from 25 married women in the childbearing age who had been treated with radium inside the uterus for uterine bleeding. Their average age was thirty-four years. Four of them reported pregnancy after the treatment, 2 of them going to full term, 1 had a premature labor at seven and a half months due to eclampsia and the other miscarried at the third month. Therefore, Pemberton states that it is evident that a patient can be treated with radium and bear normal children subsequently. He has no data on whether or not such treatment decreases the chance of becoming pregnant in women who wish children and it would be difficult to get reliable information. It is probably true that deformed or underdeveloped children are not likely to follow such treatment. A damaged ovum is not capable of

being fertilized, or if it is, it probably results in a blighted ovum which comes away by miscarriage. It is important to examine the products resulting from such miscarriages to find out if the fetus is absent or deformed. Care should be taken not to treat pregnant women, because it may cause interference with the growth of the fetus.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA.

AND

W. L. HOLMAN, M.D.,

ASSISTANT PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA.

The Effect of Thyroxin on the Cutaneous System in the Sheep.—SIMPSON (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 572) observed that, following the administration of thyroxin to an eight-months-old, thyroidectomized lamb, the fleece began to fall out until, in the course of twenty-days, the whole animal was bare to the skin, save for the head and neck. The thyroxin was given, originally, in doses of 0.5 mg. to save the animal's life. As the lamb improved, the dose was diminished to 0.25 mg. and then to 0.125 mg. The shedding of the wool began about one month after the initial dose of thyroxin. Two normal sheep were then inoculated with thyroxin. One sheep showed no effect while the other, in about a month, reacted as the thyroidectomized lamb had done, only to a lesser degree.

Production of Goiter in Rats by Restricted Iodin Feeding.—HAYDEN, WENNER and RUCKER (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 546) divided two litters of white rats, half of each being placed in a separate cage. All the rats were fed a diet consisting of 53 parts oats, 25 parts patent flour, 20 parts linseed meal, 1 part calcium phosphate and 1 part sodium chlorid. One group was given distilled water to drink, and the other, water containing 0.1 mg. of iodine per liter. Two rats on each diet were killed after four weeks and the thyroids weighed. This procedure was repeated every two weeks until all had been killed. It was found that the thyroids in those rats not receiving iodine were twice as large as they were in the other group.

The Effect of Anesthesia and of Sedatives on the Serum Therapy of Experimental Botulism.—The rapid progress of the intoxication in severe cases of *botulinus* poisoning in man has rendered of questionable value the therapeutic use of antitoxin in such instances. In the course of a series of experiments designed to investigate the path of absorption of *botulinus* toxin, BRONFENBRENNER and WEISS (*Jour. Exper. Med.*, 1924, 39, 517) observed that guinea-pigs under ether anesthesia remained alive for hours after the death of unanesthetized guinea-pigs that had

received a similar amount of toxin. Because of the importance attached to any method delaying the intoxication in botulism, the authors investigated the influence of ether and other drugs minutely. It was found that when guinea-pigs were fed large quantities of *botulinus* toxin they developed symptoms of intoxication within six hours and usually died within twelve hours after the feeding of toxin. And, if very large amounts of toxin were introduced intraperitoneally, the animals died, as a rule, within two hours. If, however, the guinea-pigs were etherized, their life was prolonged by a period approximately equal to that during which the administration of the anesthetic was continued. The giving of the ether delayed the progress of intoxication but did not alter the toxin or the nature of the mechanism of intoxication—not only when administered immediately after the intake of toxin but when administered much later, after the intoxication had progressed far enough to cause definite objective symptoms of poisoning. Similar results were obtained with luminal sodium, nitrous oxide—oxygen mixture and morphin. The authors conclude by saying that “in view of the fact that the published data indicate that *botulinus* antitoxin has thus far failed to give beneficial results in the treatment of botulism in human beings because, as it would seem, of the rapid progress of intoxication, any method of delaying the progress of intoxication to supplement the antitoxin therapy deserves consideration.”

The Biological Action of the Beta Rays of Radium.—“Methods of radium therapy commonly employed consist in the application of the radium over the surface of the area to be treated or in the insertion into the tissue to be influenced of metal needles containing radium. In both instances the radium rays are filtered in such a manner that only the gamma rays penetrate into the tissues and act as a therapeutic agent.” By collecting radium emanation in capillary glass tubes from 1 to 5 mm. long and 0.25 mm. in diameter and inserting these tubes into such structures as normal liver, spleen and bone marrow of rabbits, muscles and testicles of rats and mice, sarcoma of rats, carcinoma of mice, young plant tissue, crown galls of geranium and club roots of cabbage, LEVIN (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 462), working in coöperation with Michael Levine, was able to make a gross and microscopical analysis of the irradiated tissues to determine the effect of both the beta and gamma rays. It was found that the zone of tissue immediately surrounding the glass capillary was in a state of complete necrosis. The second zone showed characteristic gamma-ray irradiation changes in the protoplasm and nuclei of the cells. This latter zone was more extensive in tumor than in normal tissues. In addition, tissues obtained on clinical material were studied at various intervals after the insertion of the glass capillaries. Not only were the clinical results very significant but pathological conditions, which did not yield to large quantities of filtered rays, responded readily to beta-ray action. The author indicates that the beta-ray action is not a caustic one, but is qualitatively analogous to the action of the gamma rays. After a discourse of the present-day conception of the physics of the various rays, he says that “the biological action of the gamma and beta must be analogous.” “The difference is quantitative and is due to the fact that the ratio of beta and gamma rays in a unit of radium is about

100 to 1. Five millicuries of radium emanation distributed to 10 capillaries will destroy 10 cm. of carcinoma. To produce the same effect by surface application the gamma rays of 500 mc. would have to be employed. The statement made by physicists that the biological effect of 1 mc. of radium emanation buried in the tissues equals 132 mc. hours of surface application of filtered radium must be corrected since it does not take into account the action of the beta rays and their secondary roentgen-rays."

Observations on Some Causes of Gall-stone Formation. I. Experimental Cholelithiasis in the Absence of Stasis, Infection, and Gall-bladder Influences.—ROUS, McMASTER and DRURY (*Jour. Exper. Med.*, 1924, 39, 77), in reporting their observations on lithiasis developing in dogs permanently intubated for the collection of sterile bile, as described by ROUS and McMASTER (*Jour. Exper. Med.*, 1923, 37, 11), say "whatever the significance of our findings, or lack thereof, there can be no doubt that the problem of cholelithiasis waits upon the development of an experimental material." The literature of the subject has been "from early times a literature top-heavy with hypothesis and dismal with uncorrelated observations." Gall stones developed in 14 out of 22 intubated dogs. The stones were formed from liver bile. Thirteen of the animals were kept with special reference to maintenance of health, and in 7 of these calculi developed. Four of this number had daily sterile cultures of bile. The secretion had become infected in 4 of the 6 animals which did not show stones at autopsy. "Nine intubated dogs were submitted to procedures that may have, and often undoubtedly did, produce pathological changes in the secretion, as for example, the intravenous injection of hemoglobin or calcium chlorid, prolonged chloroform anesthesia, and toluylenediamin poisoning. Seven of these developed calculi. The bile was infected in only 2 of these 7 instances of lithiasis and in 1 of the 2 dogs that were free from stones. The stones always occurred in the system of glass and rubber tubes which connected with the common duct and developed as early as fourteen days after intubation. In general the stones exhibited little variety of structure and composition as compared with human stones. three general types of stones could be discriminated, one consisting almost wholly of calcium bilirubinate, another of calcium carbonate, and a mixed type in which both compounds were present. The stones were found not to be the result of bile loss." In a companion essay, ROUS, DRURY and McMASTER (*Jour. Exper. Med.*, 1924, 39, 97) reported the results of a study of the early history of the gall stones with special reference to the role of preformed nuclei in their development. Utilizing the same material, the authors found that only very occasionally did the calculi form in the absence of a special center of deposition. Sometimes a particle of talc from the wall of the rubber collecting tube served as a nucleus, but more often the calculus formed in the midst of small masses of organic debris, or deposition of the salt occurred upon the surface of bilirubinate calculi. After reviewing at some length the factors concerned in the genesis of gall stones consisting of calcium carbonate, the authors believe that their evidence supports the view that the development of carbonate stones in human beings as well as in the dog may be a consequence, not of changes in the bile

brought about by microorganisms, nor of the elaboration of an inflammatory exudate rich in calcium salts, but, merely of inflammation such as leads to lessened motility of the duct system with the accumulation of organic debris. "The fact that infection is almost the sole agent whereby such inflammation is set up and maintained in clinical instances has led too often to the conclusion that it serves as the essential agent in the process of calcification." Continuing their detailed observations on some causes for gall-stone formation, DRURY, McMASTER and ROUS (*Jour. Exper. Med.*, 1924, 39, 403) reported certain experimental findings having to do with the relation of the reaction of the bile to experimental cholelithiasis—or, as they aptly put it "with the reasons for the absence of such stones from dogs with an intact biliary tract." There are several evident safeguards against stone formation within the ducts, as they have suggested, "their motility, the cleansing and possibly antagonistic action of the secretion they themselves elaborate, and the flushing out effected by an intermittently quickened bile stream." "But how is one to explain the absence of calculi from the gall-bladder, a viscus which, according to the latest evidence, empties itself but poorly, and in which the bile often undergoes great concentration and must frequently be held for many hours together." "In view of the marked tendency for calcium carbonate to come down out of liver bile on standing, and for it to deposit within old organic debris, it seems certain that the normal gall-bladder must either effect some change in the secretion in the direction of safety, or else add some preventative against deposition." The solubility of calcium carbonate is known to be markedly affected by the reaction of the fluid in which it is contained. The normal liver bile, out of which it tends to precipitate, is alkaline, with an average pH of 8.20 but in the gall-bladder where conditions might otherwise seem especially favorable to precipitation, the secretion undergoes a change toward the acid side, becoming on long sojourn there, strongly acid to litmus (pH 5.18 to 6.00). From bile thus altered, no carbonate precipitation occurs, even when it becomes greatly concentrated as in fasting animals or after obstruction of the common duct. The authors conclude by stating that "the possibility that cholelithiasis may be a consequence of sins of omission on the part of the biliary channels and reservoir deserves to be considered."

Seasonal Changes in Organ Weights and their Relation to Meteorological Conditions.—"It is well known that many of the endocrine glands of normal animals undergo rhythmic changes in weight per unit of body weight which conform, in general, with seasonal conditions." Since the cause of these changes is not clearly understood, BROWN, PEARCE and VAN ALLEN (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 373) studied the ratio of the weights of various organs and tissues to the body weight of normal rabbits and the limits of variation which might be encountered. The factors studied included age, breed, length of caging, time of killing (with reference to the regular system of feeding), and meteorological conditions. All the animals were males and were fed on a uniform diet of hay, oats and cabbage. Two groups of rabbits selected from stocks that were being used for experimental work, were killed each month and the various organs were weighed. The weights were then reduced to terms per unit of net body weight which was

determined by subtracting the weight of the gastro-intestinal mass from the live weight of the animal with additional allowance made for excess urine in the bladder. All the organs examined were found to undergo rhythmic changes in weight per unit of net body weight which conformed, in general, to the progression of the seasons. In the case of organs such as the heart, kidneys and liver, the transition from one condition to another occurred relatively slowly (20 to 40 per cent), and the maximum variation in any direction was distinctly less than that noted in the case of a number of the endocrine glands and the lymphoid tissue (50 to 100 per cent). On attempting to correlate this series of seasonal variations in organ weights with meteorological conditions, it was found that the majority of them corresponded in time and direction with prevailing conditions of sunlight. In general, the periods of maximum and minimum weights coincided with high or low levels of daily sunlight while the change in direction and the transition from one condition to the other corresponded with the change in sunlight from winter to summer or from summer to winter. It appeared that the weight curves of some organs conformed more closely to the curve of temperature or to humidity than to the curve of sunshine, and that the degree of correlation in any case was subject to the influence of other factors. The authors were able to deduce from their observations that no fixed relationships exist between the various organs and tissues of the body—that mass relationships and probably functional activities are subject to continuous change in response to certain external influences such as are represented by climate or meteorological conditions; that these changes tend to pursue a rhythmic course in harmony with the progression of the seasons, but that they are retarded or accelerated or otherwise affected in accordance with the prevailing meteorological conditions; and that, in considering the influence of factors of this kind, there are two things to be taken into account, namely, the normal or prevailing level of activity and the factor of change.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Observations on the Presence of a Toxic Substance in the Blood and Urine of Patients with Scarlet Fever.—TRASK and BLAKE (*Jour. Exper. Med.*, 1924, 40, 381) state that a series of observations on the blood of patients acutely ill with scarlet fever has shown that a toxic

substance can be demonstrated in the serum by means of intracutaneous injections of the serum in persons who have not had scarlet fever and whose serums fail to blanch the rash in scarlet fever. The reaction caused by this substance consists of a bright red local erythema, varying from 20 to 70 mm. in diameter, of one to four days' duration. The severer reactions are moderately indurated and tender and are followed by pigmentation and desquamation. Control injections in persons whose serums blanch the rash in scarlet fever cause no reaction. The toxic substance is not neutralized by mixture with a human serum which gives a negative blanching test but is readily neutralized by a human serum which gives a positive blanching test. It is not neutralized by normal horse serum but is completely neutralized by Doehez's scarlatinal antistreptococcic serum. In a limited number of observations on the urine of patients with scarlet fever a similar toxic substance has been found in 2 out of 5 cases studied. Since the toxic substance described appears to resemble the toxic substance found in the filtrates of scarlatinal hemolytic streptococcus cultures by Dick and Dick, and since it is neutralized not only by a blanching human serum but also by Doehez's scarlatinal antistreptococcic horse serum, the experiments reported support the conception that scarlet fever is a local infection of the throat by a particular type of *Streptococcus hemolyticus* capable of producing a toxin which is absorbed and is the cause of the general manifestations of the disease.

Inflammatory Reaction of the Immune Animal to Antigen (Arthus Phenomenon) and Its Relation to Antibodies.—OPIE (*Jour. Immunol.*, 1924, 9, 231) says that local anaphylaxis or the Arthus phenomenon is an inflammatory reaction which occurs when an animal immunized against a protein is reinjected with the same antigen; it is caused by an antibody present in the blood serum and tissues of the immunized animal and occurs when antigen and antibody meet in the tissues. This reaction which varies in intensity in different species of animals, and may fail to occur in some (rat, dog), bears a close but not exact relation to the ability of the animal to form precipitin. An animal passively immunized by injection of serum of an immunized animal exhibits the reaction which may be so severe that necrosis occurs. Simultaneous injection of antigen and of serum from an immunized animal causes acute inflammation at the site of injection. In animals with either active or passive immunization there is a very close but not exact parallel between precipitin content of the serum and the occurrence and severity of specific inflammation. The discrepancies observed do not exclude the possibility that precipitin is the antibody concerned.

Immunological Studies in Tuberculosis: II. Further Observations on Skin Hypersensitiveness in Experimental Tuberculosis.—PETROFF (*Jour. Immunol.*, 1924, 9, 309) says that true tuberculin skin hypersensitiveness can be set up in a normal animal by the injections of tubercle bacilli killed at 100° C. for one hour. From unpublished work he has further proof that the substances responsible for setting up true hypersensitiveness are not even destroyed by heating for a half hour at steam pressure at one atmosphere (121° C.). The success

of this sensitization depends on the following few points: The tubercle bacilli must be triturated well, made up in good suspension, and the reaction adjusted to pH 6.9 or 7.0 before sterilization. Above all, one of the most important points is that animals suitable for such sensitization must weight 400 gm. or over. They must be well fed and kept in good condition. The injection should be made every three or four days. It seems, so far, that the intraperitoneal route is the most suitable one. After each injection of killed tubercle bacilli there is a distinct drop in the weight of the animal. In a day or so the animal again picks up his weight, but the drop follows after subsequent injections, and as soon as the three injections have been made, the animal gradually recovers the loss and begins to gain very rapidly. It is an interesting observation that if the animal suddenly begins to lose weight the skin hypersensitiveness also diminishes somewhat.

Microbic Virulence and Host Susceptibility in Paratyphoid-enteritidis Infection of White Mice: V. The Effect of Diet on Host Resistance.—WEBSTER and PRITCHETT (*Jour. Exper. Med.*, 1924, 40, 397) found that white mice from the Rockefeller Institute breeding-room fed on a McCollum complete diet, consisting of whole wheat (67.5 per cent), casein (15 per cent), milk powder (10 per cent), NaCl (1 per cent), CaCO_3 (1.5 per cent) and butter fat (5 per cent) are more resistant to mouse typhoid infection, mercury bichlorid intoxication, and botulinus toxin than are similar mice fed on bread and pasteurized milk supplemented by an oatmeal and buckwheat mixture and dog biscuit.

A Histological Study of the Central Nervous System in Experimental Botulinus Poisoning.—COWDRY and NICHOLSON (*Jour. Exper. Med.*, 1924, 39, 827) says that the results of their observations indicate that, except for a slight degree of vascular engorgement, all the lesions which they have noted in the brains of mice, guinea-pigs and rabbits suffering from botulinus poisoning are readily susceptible of some explanation other than that they are produced by the direct action of the toxin upon the central nervous system. This absence of microscopical evidence of a central action of the toxin is not, of course, conclusive proof that the cells in the brain are not primarily involved, because it is quite conceivable that, owing to the delicacy of the nervous mechanism, the toxin might well act centrally without leaving any traces microscopically visible. But the observations do not tend to show that, upon the histological side, there is no evidence inconsistent with the results of physiological experiments indicating that the site of action of the toxin is upon peripheral nerve terminals.

Transmission of a Flagellate Infection from Plant to Animals.—STRONG (*Am. Jour. Hyg.*, 1924, 4, 345) has shown that a flagellate which produces a disease in plants (*Euphorbiæ*) may be passed through an invertebrate, the lizard (*Cnemidophorus lemniscatus*). An insect (*Chariesterus cuspidatus*) transmits the infection from the plant to the lizard. From the invertebrate host it was transmitted to a monkey, in which it gave rise to a form of tropical ulceration in the skin. In this ulceration the leishmania form of the parasite and not the flagellate stage is encountered. This is the first time a chain of infection due to

a parasite primarily producing a disease in plants has been shown to pass through an invertebrate to a vertebrate host and acquire pathogenic properties for mammal. We here see the evolution of disease in the making.

The Relation of Vegetative Activity of Bacteria to Pathogenicity.—FELTY and BLOOMFIELD (*Jour. Exp. Med.*, 1924, 40, 703) report experiments showing that distinct differences exist between relatively young cultures of bacteria and the same strains during the period of decline as regards invasive power and pathogenicity, and that these differences must be distinguished clearly from specific alterations in virulence such as those produced by animal passage. The exact interpretation of these observations is not, however, perfectly clear. The authors are inclined to believe that simple alterations in vegetative activity might account for the differences which have been described, but to what extent the results have been due to injury to the bacteria by products of culture growth it is impossible to say, and further work will be necessary to settle this point. At any rate the experiments seem to bear definitely on the problem of infection in as far as they show that purely temporary modifications of growth activity, whether or not brought about by specific injury, lead to changes in invasiveness which are quite analogous to the test-tube phenomenon of lag. The authors have previously shown that there exists in the upper air passages a mechanism by means of which foreign particles and bacteria can be eliminated within a few hours. They state that it seems highly likely on the basis of their present work that bacteria entering in an inactive growth phase—for example dried in dust or perhaps from a chronic carrier—may be disposed of before activity can be resumed, whereas organisms introduced in the stage of active growth—as from a case of acute disease—may be able to take advantage of a portal of entry. It is further possible that these experiments may have some bearing on the genesis of epidemics, especially as regards the preëpidemic phase, and these matters will be discussed at another time.

Outbreaks of Botulism at Albany, Oregon, and Sterling, Colorado February, 1924.—STRICKER and GEIGER (*Pub. Health Rep.*, 1924, 39, 655) report that in the first outbreak 12 persons were affected and 8 of these died. It was found that home-canned string beans were responsible, and the interesting fact was brought out that not all the food which was toxic was obviously spoiled. The incubations period was from 16 to 40 hours and death occurred in from 27 to 103 hours. In the second instance there were 7 cases, with 5 deaths. Home-canned string beans were responsible for this outbreak also.

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All communications should be addressed to—

DR. EDWARD B. KRUMBHAR, The Laboratories, Philadelphia General Hospital, Thirty-fourth Street below Pine.

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ORIGINAL ARTICLES.

THE DIRECT EFFECT OF RADIUM IRRADIATION ON
LEUKOCYTES.*

By ROY G. SPURLING, M.D.,

AND

JOHN S. LAWRENCE, M.D.,

BOSTON.

(From the Medical Service of the Collis P. Huntington Memorial Hospital and the Laboratory for Surgical Research of the Harvard Medical School.)

HISTOLOGICAL alterations in the character of the leukocytes in the circulating blood occur following relatively large therapeutic doses of irradiation from radium and roentgen-rays. These changes for the most part, are destructive in nature; every phase of degeneration from vacuolization to complete disintegration of the white blood corpuscles has been observed. Minot and Spurling¹ have shown that following therapeutic short-wave length roentgen-ray irradiation, the degenerated leukocytes range from 10 to 40 per 100 formed white cells. They usually reach their highest level on the second day following exposure to the rays, but abnormal numbers are to be found within an hour after treatment. Whether these changes are the result of the direct effect of irradiation on the leukocytes in the circulating blood, or an indirect effect of the rays upon them, has been a matter of speculation. The experiments described below

* This paper is No. 33 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed (in part) by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

were undertaken for the purpose of attempting to obtain information concerning this subject.

Experiments were conducted on dogs under ether anesthesia and one was repeated on man. In these experiments, stasis of the peripheral blood was created, as this was necessary in order to prove that irradiation directly destroys leukocytes in the blood stream. Another experiment to determine the direct effect of irradiation on leukocytes was performed on human blood outside the body. The technique and nature of the four varieties of experiments conducted are given below:

1. A tourniquet was applied to both hind limbs of a dog at about the level of the middle of the thigh. The pressure applied was sufficient to cause venous stasis without wholly impeding the entrance of arterial blood to the extremity. An erythema dose of radium emanation was given over one leg, the other served as a control. Blood was obtained before irradiation and every fifteen minutes thereafter for one and a quarter hours by puncturing with a cutting edge needle, the deep tissues of the legs below the tourniquets. The white blood corpuscles were studied in carefully made Wright stained blood smear preparations, as was the case in the other experiments noted below. Seven experiments of this first variety were performed.

2. In the second form of experiment on dogs, a section about 2 inches long of both femoral veins was tied off in the femoral triangle. An erythema dose of radium emanation was applied over one of these segments. The ligated strip of vein of the opposite leg served as a control, and care was taken to screen it from the rays.

Samples of blood for study were obtained from each of the tied off segments by means of a small hypodermic needle before irradiation and afterward every fifteen minutes during one and a quarter hours. (No edema of either leg developed and the animal suffered no ill-effects from the ligation of both femoral veins.) One such experiment was conducted.

3. The third variety of experiment was performed twice on man. Sphygmomanometers were applied to both upper arms of a patient and the pressure kept just above the diastolic arterial pressure for forty-five minutes. Slightly less than an erythema dose of radium emanation was applied over the median basilic vein of one arm. Four samples of blood were taken directly from the vein of each arm at intervals of fifteen minutes.

4. The last type of experiment consisted of irradiating with radium emanation, equal to two erythema doses, citrated human blood placed in a flat glass dish. The citrated blood was exposed directly to the rays, thus making it unnecessary to pass the rays through glass. Then the leukocytes were examined for evidences of histological changes, every fifteen minutes for one and one-half hours.

No constant changes in the character of the leukocytes which could be attributed to the effect of irradiation were observed in any of the four different types of experiments. The number of degenerated forms was essentially the same (less than 8 per 100 formed white cells) and the differential count remained practically constant, in the preparations obtained from the area exposed to radium in the experiments on dog and man, (procedures 2 and 3 above). There was, also, no difference in the character or differential count of the leukocytes from that seen in the control samples of blood. Likewise no alterations in the leukocytes were detected when they were irradiated outside the body, (procedure 4 above).

In procedure 1, in which the blood was obtained from dogs' subcutaneous tissue, many leukocytes in every stage of disintegration were observed in several of the blood smears. In the first three animals, these broken forms were more plentiful in the smears made of the blood taken from the leg which had been exposed to radium, than in the control preparations. It thus appeared as if the irradiation was responsible for the changes. Analysis of the method of collecting the blood and similar subsequent experiments clearly showed that it was the technic by which the blood was obtained that was responsible for these disintegrated leukocytes. Four experiments in which blood was obtained by proper technic, permitted no changes from normal of any sort in the leukocytes from the irradiated and non-irradiated extremity. Thus the results of the first experiments on dogs can be reconciled as in accord with those obtained from the other studies made.

The technic that caused the presence of many disintegrated leukocytes in the blood smears from the dogs, depended upon the squeezing and manipulating of tissue. It was demonstrated at will that leukocytes of this character could be found in abundance in preparations made when the blood was obtained from skin puncture with forceful manipulation, but when a relatively large vessel was punctured so that the blood flowed freely, preparations made from it showed but a scant number of broken leukocytes. It is much more difficult to destroy white blood corpuscles by mechanical manipulation of tissue in man than in dogs. This is partly because of the known fact that dogs' leukocytes are more fragile than those of man. An additional reason is probably because blood flows much more readily from a small needle prick of the human skin than from one in a dog. We were unable to obtain after considerable manipulation of patients' tissue, more than 10 broken leukocytes per 100 formed ones in blood smears properly made on cover glasses. Of course the many degenerated leukocytes repeatedly observed in the circulating blood following therapeutic irradiation are not due to any errors of technic because it is well known that the leukocytes in similarly obtained blood smears prior to irradiation show no such changes. It seems evident that irradiation from radium does not directly affect the character of the leukocytes within

an hour and a quarter after exposure and that some indirect effect is responsible for the degenerated forms seen following therapeutic irradiation.

In our experiments, where the blood stasis persisted from three-quarters to one and a quarter hours, there were no constant changes in the differential leukocyte counts of the blood taken from the constricted extremity. In contrast to these results, Webb² has shown that there is both a relative and absolute increase in the number of lymphocytes following the application of a tourniquet to a leg of man and the hind extremities of rabbits. In his experiments on man, he found an 18 per cent increase in the number of "mononuclears" in as brief a period as a half hour, and a 75 per cent increase after one hour. His experiments, like our own, attempted to obstruct the venous return without impeding the flow of arterial blood. Calvé³ also found an inversion of the differential leukocyte count following the constriction of an extremity in man. While he does not make it clear just how long was required for this to take place, it appears that he observed this change within thirty minutes following the application of a tourniquet. Unfortunately, neither Webb nor Calvé definitely state from where the samples of blood were obtained. It would appear, however, that they were taken from the general circulation and not from the isolated extremity. If this was the case, their experiments were not parallel to our own, as we obtained samples of blood from a point below the tourniquet where blood presumably had been isolated, which did not become mixed with that of the general circulation during the period of the experiment. It is difficult for us to see why the differential count of white cells in the blood of an extremity should change markedly in a brief period of time, even if one accepts the theory of mitotic division of lymphocytes. On the other hand, it is quite conceivable that a relative and absolute lymphocytosis may occur in the general circulation following the constriction of an extremity.

Summary. 1. Radium irradiation of blood retained in an extremity of a dog or man, or in a vein of a dog, produced no demonstrable changes in the character of percentage numbers of the different types of leukocytes in one and a quarter hours. Likewise the stasis of blood in an extremity or vein for a similar period of time was without effect on the leukocytes.

2. The manipulation of dogs' superficial tissues in obtaining blood, produces destruction of leukocytes much more readily than similar trauma in man.

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REPORT ON A CASE OF MALIGNANT SMALL-CELLED THYMOMA WITH ACUTE LYMPHOID LEUKEMIA.

BY ALFRED FRIEDLANDER, M.D.,

AND

NATHAN CHANDLER FOOT, M.D.

(From the Departments of Medicine and Pathology, Cincinnati General Hospital, and College of Medicine, University of Cincinnati, Cincinnati, Ohio.)

Introductory. Cases of malignant thymoma are so obscure, and of such rarity, that they should be reported and discussed whenever encountered. This example illustrates a particularly unusual variety of the tumor, the small-celled, sarcomatoid type with metastasis to distant organs and a concomitant lymphoid leukemia. Ewing. (1922), in his text-book "Neoplastic Diseases," cites a few instances of widespread metastasis involving the liver, spleen, kidney, adrenal, and pancreas and refers to an article by Fabian in which a considerable series of cases has been reported, with a leukemic blood-picture as the chief clinical feature, associated with large sarcomatous tumors of the thymus. Such leukemias are considered atypical and especially malignant. As a rule thymomas tend to be limited to the anterior mediastinum and immediately contiguous organs. The points indicating the thymic origin of mediastinal sarcomas, as set forth in the literature on this subject, may be summed up as follows: (1) The situation of a large, not much lobulated, firm tumor at the site of the thymus; (2) extension downward behind the sternum, without infiltration of the bone; (3) involvement of the pericardium and pleura by direct lymphatic extension; (4) a resemblance to thymic tissue on histological examination. In connection with the last point, some authorities insist that all the histological elements of the thymus be found in some form, but usually a resemblance of the dominating type cell to one or other thymic element is accepted as sufficient evidence. The tumor we are reporting fulfils all of these conditions with the exception of the third—it does not involve the pleura, although intimately connected with the pericardium, metastasizing rather, to distant organs.

1. CLINICAL CASE REPORT.

BY ALFRED FRIEDLANDER, M.D.

The following is a condensed protocol of the clinical history of the case:

History of Case. E. B., a colored female, aged thirty-eight years, married, was admitted to the West Medical Service of the Cincinnati

General Hospital November 4, 1923. Her chief complaint was a "painful swelling of the right leg."

Present Illness. Ten days before admission the patient had experienced a sudden sharp pain in the upper portion of the right thigh. Within a few hours, the thigh was much swollen. The pain continued and the swelling increased—so that within twenty-four hours, thigh, leg and foot were swollen to about twice the normal size. The pain and swelling continued unchanged for about a week—so that the patient was bedfast. She was admitted to hospital about a week after the onset—by which time the swelling had decreased to some extent, though the pain on movement of the extremity was still severe.

Past History. The patient had had a severe pneumonia six years before the present illness. She had had several attacks of tonsillitis during the last three years, and an appendectomy three years before present illness. She denied venereal infection; had been married eight years, but had never been pregnant.

Admission Physical Examination. Temperature, 101.2; pulse, 120; respiration, 24. A poorly developed, moderately well-nourished woman, apparently acutely ill, complaining of severe pain in right thigh. Eyes, ears, nose, negative.

Mouth: Lips smooth, tongue dry and coated, protruded in midline without tremor. *Teeth:* Very poor with many carious snags, and some evident pyorrhea. *Tonsils:* Enlarged but not acutely inflamed, not cryptic. Gray streak in right tonsil.

Neck: No rigidity, no tenderness, no enlargement of thyroid.

Heart: Apex beat visible and palpable in the 5th interspace, 6.5 cm. to the left of the midsternal line. Not diffuse. No thrill, no shock. Cardiac conjugates 3.5 by 8.5 cm. Retrosternal dulness in first interspace, 6 cm. Sounds clear at apex and base, no murmurs, no arrhythmia. The second pulmonic sound was slightly louder than the second aortic, but not accentuated. Radial pulse equal, volume and tension fair. Blood-pressure, 122 over 80.

Lungs: Percussion note clear throughout, breath sounds vesicular. No rales. Spoken and whispered voice normally transmitted.

Abdomen: On level with chest, no enlargement of liver or spleen. Slight tenderness in right inguinal region. None elsewhere.

Genitalia: Right labium majus swollen. In the introitus there was a moderate sized serpiginous ulcer with marked induration about it. The uterus was enlarged and fixed in the pelvis. There was a moderate sized fibroid.

Extremities: Right thigh and leg swollen and painful. No open ulceration. Some pitting on pressure in leg and foot. No marked limitation of motion in the joints. The tenderness was more marked on the inner aspect of the thigh and leg.

Comparative measurements of the two extremities:

	Right, cm.	Left, cm.
Mid thigh	48.0	40.0
Mid leg	33.0	25.5
Ankle-joint	25.5	18.0
Foot	21.0	18.0

Glands: No generalized adenopathy. The inguinal glands on the right side are slightly enlarged and tender.

Reflexes: All the deep reflexes are normal.

Blood Examination: Erythrocytes, 3,100,000; leukocytes, 140,000; hemoglobin, 60 per cent. Differential Count: (300 cells) lymphocytes, 93 per cent; large mononuclears and transitionals, 2 per cent; polymorphonuclears 4 per cent; basophiles, 1 per cent. There is moderate anisocytosis. The predomination of the lymphocytes is apparent. Some Rieder cells are found. There appears to be slight increase in number of platelets.

Urinalysis: Reaction alkaline; albumin present; a few granular casts and some red and white blood cells.

Blood Wassermann: Strongly positive. (Confirmed by second test three days later.)

Blood Chemistry: Blood sugar, 143 mg.; urea nitrogen, 28 mg.; uric acid, 42 mg.; chlorids, 470 mg. per 100 cc.

Provisional Diagnosis: (1) Thrombophlebitis of right internal saphenous vein, possibly dependent on pelvic injection; (2) lymphoid leukemia, acute; (3) lues.

It is noteworthy that, at the time of admission there was no enlargement of liver or spleen, no increase in retrosternal dulness, and no generalized adenopathy. A portion of the ulcer of the introitus was removed. Examination showed no evidence of malignancy. (See detailed report in pathological section.) Blood cultures taken seven and ten days after admission were sterile.

Clinical Course. The temperature ran a somewhat irregular course, ranging from 100° to 102° without particularly typical curve, up to the time of death.

The blood-picture showed a constant increase in the number of white cells, with a decrease in the reds as shown in the following table:

TABLE I.—COURSE OF BLOOD-PICTURE.

Date.	Leukocytes.	Erythrocytes.
Nov. 4, 1923	140,000	3,100,000
Nov. 6, 1923	150,000	
Nov. 11, 1923	170,000	2,800,000
Nov. 22, 1923	208,000	1,920,000
Nov. 30, 1923	252,000	
Dec. 5, 1923	320,000	1,568,000

Detailed description of blood smears taken on November 4 and December 5 will be found in the pathological report.

On November 14, ten days after admission, it was noted that there was some increase in the retrosternal dulness. This was sufficiently marked to suggest the advisability of chest radiographs. The radiological report of that date noted that there was "considerable increase in the width of the shadow in the anterior mediastinum suggesting an enlarged gland."

On November 26 it was noticed that the abdomen seemed somewhat distended. At this time the liver edge could be felt 6 cm. below the costal margin. The spleen was not enlarged. From this time on the increase in the size of the liver was rapid until by November 30 it was noted that the border of the right lobe extended to the umbilicus. Two days later the patient began to complain of pain in the left cheek. Examination showed a gangrenous stomatitis of the left buccal surface extending to the tonsil. Covering this was a dirty gray, patchy membrane. Fetor was extreme. Examination of smears, made from the membrane repeatedly, were negative for the organisms of Vincent's angina and for Klebs-Löffler bacilli.

With the advent of gangrenous stomatitis the temperature became higher and the patient's suffering greater. At this time the cervical glands were only slightly enlarged.

On December 8, it was noted for the first time that the spleen was palpable. Both liver and spleen increased in size steadily up to death.

The treatment consisted of rest, elevation of the thigh, full doses of neosarsphenamin (12 intravenous injections) with local treatment for the mouth, sedatives and anodynes.

Final Clinical Diagnosis. Thrombophlebitis (right saphenous); acute lymphoid leukemia; enlarged mediastinal glands; enlargement of liver and spleen; uterine fibroid; lues; luetic ulcer right labium majus.

2. PATHOLOGICAL STUDY.

BY NATHAN CHANDLER FOOT, M.D.

Condensed Necropsy Protocol. Necropsy 23-292, forty-five-minutes postmortem.

ANATOMICAL DIAGNOSIS. Malignant thymoma, lymphoid leukemia, metastatic tumors of kidneys, retroperitoneal nodes, and inferior cava. Thrombosis of inferior cava. Diffuse infiltration of liver with lymphoid (?) tissue. Healed appendectomy wounds. Leiomyomas of uterus. Chronic salpingitis, with bilateral adhesions. Gangrenous glossitis, stomatitis, and gingivitis. Edema of right labium majus. Vaginal ulcerations.

Body. Is that of a well-built, fairly well-nourished colored woman 150 cm. in length. It is still warm, and rigor mortis has not set in. Externally, the only interesting pathological features are

the condition of the mouth and the presence of an appendectomy scar over McBurney's point, together with swelling of the right labium majus and right leg. The left buccal cavity and the left half of the under portion of the tongue are converted into gangrenous sloughs, grayish-green in color and indescribably foul-smelling. The gingival margins show numerous phagedenic ulcers, which are equally foul.

PRIMARY INCISION. The usual incision reveals little subcutaneous fat and rather poorly-developed musculature. The liver is very low, presenting 11 cm. below the free margin of the ribs. The uterus shows a small, spherical tumor perched on the fundus and the oviducts are thick and tortuous, bound down by numerous fibrous adhesions which connect them intimately with a coil of ileum. The diaphragm is at the fourth interspace on the right, the fifth on the left. The sternum is readily removed. Both lungs retract, exposing the lower portion of the pericardium and a large, whitish, finely-lobulated tumor, or mass, that overlies it above in the midline. This mass measures 10 x 6 x 5.5 cm., corresponding with the thymus in outline and situation. It has indications of lobules at its sharp borders and is tough and leathery in consistence. Posteriorly, it is intimately connected with the pericardium and cannot be separated from it. It surrounds the great vessels without infiltrating their walls; they run through tunnel-like passages in the tumor tissue. There is no involvement of the pleura and the hilic nodes are not incorporated in the mass, although those of the anterior mediastinum are surrounded by the growth and appear as softer, yellower areas on the section surface. The tumor is almost dead-white on section, but slightly marked by fibrous striæ. Its postero-inferior surface is smooth and spread over the pericardium, terminating below and laterally in very sharp margins. There are a few fibrous adhesions over either lung, but no evidence of tumor infiltration.

THORACIC ORGANS. Organs of Mouth and Neck: The tongue is almost half destroyed by a gangrenous process which has penetrated to the midline, near the frenum on the left, the dorsum is scarcely affected. The buccal mucosa adjoining the tongue on the left shows extensive sloughing ulcerations. The esophagus, larynx, trachea, thyroid, and cervical nodes are not abnormal, excepting that the latter are very slightly enlarged.

The heart and lungs are in no way remarkable.

ABDOMINAL ORGANS. The gastroenteric tract, the pancreas, adrenals, and femoral bone marrow are not remarkable, except that the appendix is lacking, its site being marked by a well-healed, stellate scar on the caput coli.

Spleen. 240 gm. It is large and soft and its capsule is rather tense, but not thickened. On section, the pulp is found to be soft, stripping rather easily on the knife blade and of a brick-red color,

with numerous whitish dots, representing the splenic corpuscles, over its surface.

Liver. 1610 gm. It is smooth and shining externally, its cut surface exhibits numerous whitish-yellow lines which form a reticulated pattern on a reddish background. Its consistence is normal. The gall-bladder lies in a fenestrum in the margin of the right lobe, being visible on the upper surface thereof. It contains much yellowish, rather viscous bile, readily expressible through the papilla of Vater.

Kidneys. Right weighs 120 gm., left 140 gm. They are large and pale and both of them liberally bespotted with whitish areas, some large and sunken, others small and flush with the subcapsular surface, or barely projecting above its level. The capsules strip with ease, except from these areas, where they adhere slightly. The largest of them measures 4 x 4 cm., one being situated in either lower pole. They are granular, white, with a slightly pinkish zone at the margins. Most of the other areas are rather vague in outline, suggesting tumor infiltration, rather than infarcts. The parenchyma of the kidneys is in no way abnormal, the markings distinct and the cortex not thinned out, but the whitish areas are found to extend into the latter as rounded or pyramidal masses for about 2 cm. The pelvic walls are thickened and of brawny consistence, dead-white in color and suggest tumor infiltration. They measure 3 mm. in thickness. The ureters are not abnormal.

Vena Cava Inferior. This presents a cylindrical mass of firm, yellowish-white, tough, homogeneous material in the form of a thrombus, resembling a stalk of bleached asparagus in its appearance and tapering at its upper extremity, which lies near the hilum of the right kidney. It is attached near the confluence of the iliac veins by a pedicle 10 by 4 mm. in size, its long axis corresponding to that of the vein. This point of origin overlies an enlarged retroperitoneal node that is adherent to the wall of the vein and has apparently infiltrated it. Neither iliac vein is enlarged.

Retroperitoneal Lymph Nodes. These, as well as those of the mesentery and mesocolon, are all slightly enlarged, firm, pale, and homogeneous on section.

Pelvic Organs. The uterus presents two obvious leiomyomas, one subserous, perched on the fundus, 1 cm. in diameter; the other occupying the anterior uterine wall, in which it is interstitial. It measures 5 cm. in diameter and presents the usual fibroid structure on section. The oviducts are tortuous and thickened and their fimbriated extremities are buried in fibrous adhesions. They measure 2 cm. in diameter. The ovaries are fibrosed and white. The vagina exhibits two ulcers in the anterior aspect of the left fornix, each about 1.5 cm. in diameter. They are pale, partially healed and not markedly inflamed. The urinary bladder is small, clean and not pathological.

Microscopical Description. *Microscopical Diagnosis.* Malignant thymoma of the small-celled type, with metastases to kidneys; wall of vena cava, inferior; vaginal fornix, and tonsil. Acute lymphoid leukemia. Thrombosis of inferior cava, healed apical tuberculosis, pulmonary compression and compensatory emphysema, anthracosis. Diffuse infiltration of splenic pulp by lymphoblasts, with chronic passive congestion. Chronic passive congestion of liver, with central necrosis. Diffuse lymphoblastic infiltration of lymph nodes and lymphoid tissue. Chronic fibrous tonsillitis (?). Epithelial duct inclusions in retroperitoneal lymph nodes. Cystic dilatation of pancreatic ducts. Subacute glomerulonephritis. Leiomyoma and cellular hyperplasia of uterus. Colloid goiter.

Antemortem Blood-smears: Two of these, both stained by Wright's method, and made on November 4 and December 5, 1923, respectively, were submitted to the Department of Pathology for inspection.

Smear of November 4: The total white count at this time was 140,000. One is first impressed by the large numbers of shadows, or phantoms in the smear. These measure 16μ to 24μ in diameter.

They correspond to the large predominating lymphoblasts in size and staining properties. The chief cells of the smear are rounded or ovoid, have nuclei which fill the cytoplasm almost completely, the latter forming a light-blue zone at one side. The nucleus is rounded, violet-pink, more or less dense and diffuse, with numerous vacuoles, usually more than two or three. The type is that of an immature lymphoblast. In one of these slides mitotic figures were observed in two of these cells, Fig. 1 shows a beautiful diaster. This is surely a rarity in blood smears. Variants of the type-form are noted: (a) Cells resembling these, but possessed of a darker nucleus and a brilliant china-blue cytoplasm; (b) binucleated forms, (Fig. 2) corresponding with the type cell, but containing two nuclei which lie like cotyledons, rounded at the periphery and flattened where they are apposed. The average diameter of these three types of lymphoblast is 10μ to 16μ . There is a fourth type, which should be placed in the same category, with the same measurement, but a smaller nucleus and a wide zone of cytoplasm which contains five or six violet (azur) granules. These four types would probably be classed by Downey (1923) as immature and leukocytoid lymphoblasts, the latter term applied to variety "a". The larger cells of the fourth type are known by German writers as "Riederformen."

Small lymphocytes are present, measuring 5μ to 6.75μ , and presenting nothing abnormal. Neutrophile polymorphonuclears and transitional leukocytes are found in small numbers and also appear to be normal.

The red cells present marked poikilocytosis and anisocytosis, and are pale at the center. Among these are a few young normo-

blasts with distinctly marked karyosomes, still fewer with pyknotic nuclei. The type cells do not take the oxydase stain, although the polymorphonuclears do.



FIG. 1.—Blood smear, Wright's stain, $\times 1000$. Immature lymphoblasts, one of which exhibits a diaster. A normal polymorphonuclear neutrophile in the field will serve to indicate the size of these cells.

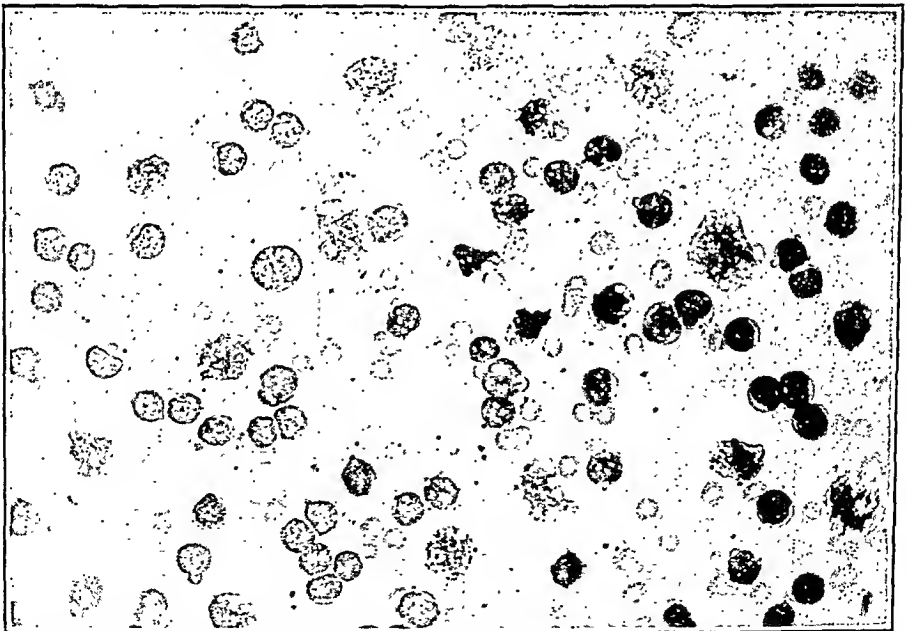


FIG. 2.—Blood smear, Wright's stain, $\times 500$. A binucleated lymphoblast lies near the center. The large vacuolated objects are lymphoblast shadows, or degeneration forms.

A differential count of 500 cells in this smear comes out as follows: Immature lymphoblasts, 68.6 per cent; leukocytoïd lymphoblasts, 0.2 per cent; binucleated lymphoblasts, 0.0 per cent; shadows, 14.4 per cent; neutrophile polymorphonuclears, 1.6 per cent; transitionals, 0.4 per cent; endothelial leukocytes, 0.0 per cent; basophile polymorphonuclears, 0.0 per cent; eosinophile polymorphonuclears, 0.0 per cent, normoblasts per 500 leukocytes, 0.4 per cent.

Smear of December 5: This differs somewhat from the preceding. The leukocytoïd lymphoblasts have disappeared, and the immature type is somewhat more uniform in size, 13μ to 16μ in diameter, with more cytoplasm than in the other smear. The "Riederformen" are more numerous. There are many lymphocytes of both large and small type showing many azure granules in the cytoplasm and resembling ordinary basophiles at first glance.

A differential count of 300 cells shows: Immature lymphoblasts, 69.9 per cent; leukocytoïd type, 0.0 per cent; binucleated type, 1.7 per cent; basophile lymphoblasts, 1.7 per cent; shadows, 23.4 per cent; microlymphocytes, 3.0 per cent; basophile microlymphocytes, 0.6 per cent; neutrophile polymorphonuclears, transitionals, endothelials, eosinophile and basophile polymorphonuclears, none. Normoblasts per 300 leukocytes, 1 per cent. The total white count has risen to 320,000.

The changes noted between these two examinations may be attributed to an increased output of immature forms as death approached. The fact that no neutrophile polymorphonuclears appear in one count, and no binucleated lymphoblasts in the other, does not mean that there was none in the smears; it indicates merely, that the fields counted contained none. Some of the illustrations in an article of Downey and McKinlay (1923) might have been drawn from the cells in our case, particularly Figs. 12, 13 and 14 of their excellent color-plate.

GENERAL MICROSCOPICAL EXAMINATION. Sections were cut to 5μ in paraffine and stained with hematoxylin eosin, Giemsa's stain, van Gieson's stain, phosphotungstic acid hematoxylin; and impregnated by the Bielschowsky-Maresch method, followed by a counter-stain of the Weigert-van Gieson type (Foot, 1924).

Sections from the heart and lungs show a general flooding of their capillaries with lymphoblasts. An area of fibrosis is found in a section from the apex of one lung; surrounding necrotic débris. This may, or may not have been tuberculous in origin. The pulmonary lymphoid apparatus is atrophic, rather than hypertrophic.

Spleen. The organ shows thickening of its reticulum, dilatation of the venous sinuses, and lymphoid cells are found scattered diffusely throughout the pulp, where red cells would usually lie. These lymphocytes tend to crowd together just beneath the capsule and do not form any reticulum. A great many endothelial phagocytes are seen, filled with pigment. The trabeculæ are somewhat thick-

ened and the Malpighian corpuseles are small, vaguely outlined, and inconspicuous.

Lymphatic Organs. The topography of the retroperitoneal nodes is almost obliterated by the diffuse lymphocytic infiltration, the "germinal centers" are merely indicated by a concentration of microlymphocytes at certain points. In the medullary sinuses there are many discrete lymphoblasts, and phagocytes containing debris, erythrocytes and pigment. Cell agglomerations similar to those seen in chronic lymphoid leukemia are found, but they are composed of lymphoblasts. No tumor reticulum is noted in these nodes.

A very remarkable feature of the retroperitoneal group is the presence of epithelial ducts, composed of cylindrical or cuboidal

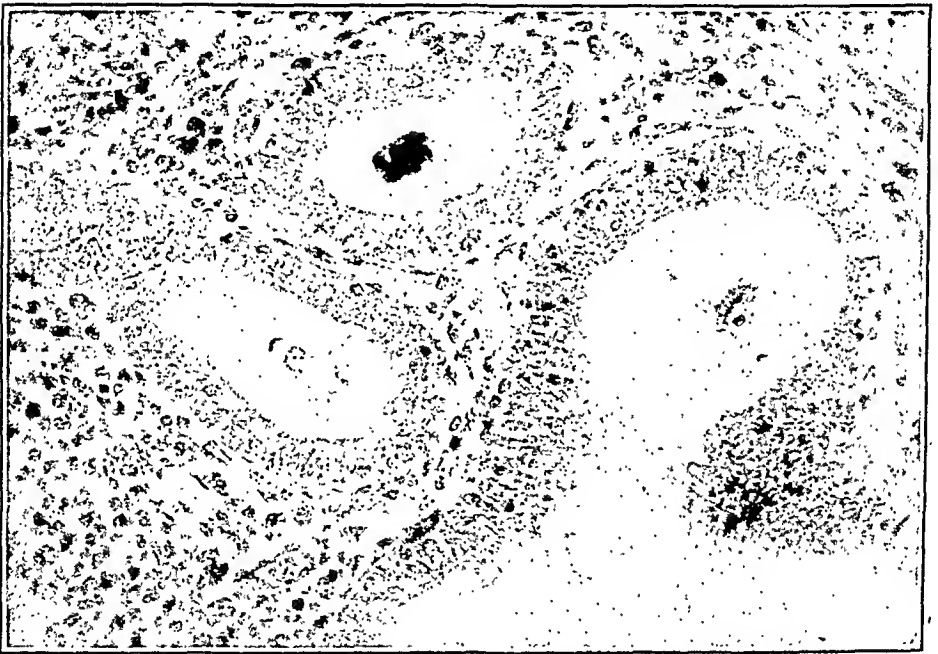


FIG. 3.—Epithelial ducts in a lymph node, Giemsa's stain, $\times 500$. Note the suggestion of cilia at the border of the epithelium.

cells with and without cilia (Fig. 3). They are sometimes distended to form cysts, too large to be brought into a high-power field and containing a granular, amorphous material. The epithelium may be simple or (rarely) stratified, and resembles that of the genital tract. These may represent endometrial inclusions in the sense of that term as used by Sampson (1921-1922) (an hypothesis materially strengthened by the experiments of Jacobson (1922)); or it may be that they are the result of fetal displacements of mesonephric tissue, which seems the more probable explanation.

Other Lymph Nodes. Some are edematous and show comparatively little abnormality, with follicles well preserved and still exhibiting "germinal centers." Many normal lymphoblasts are

seen in these nodes and a few scattered immature cells are noted. In such sections the latter are more or less polyhedral, with tail-like, trailing projections of cytoplasm, some of them possessing as much of this material as do young endothelial leukocytes.

Tonsil. This is extremely fibrotic, either because of long-standing inflammation, of tumor irritation, or on account of the production of reticulum and fibers by the tumor metastasis. Almost all of the sections show fibrous tissue and fully half of each is composed of that element. It is infiltrated by large cells resembling plasma cells (lymphoblastic plasmocytes), which are not seen in the other lymphoid organs from this case. The tonsillar crypts are well formed and contain not only débris, but also masses of lymphoid cells. The latter are chiefly found to be evenly distributed through the lymphoid tissue of the organ, as they were in the case of the lymph nodes and spleen, but some of them have formed a coarse reticulum in the tonsil, giving rise to a metastasis of the thymic tumor.

Blood Clot. This was allowed to form in the thorax at necropsy, was scooped out by hand and immediately fixed in Zenker's fluid. Sections show it to contain the elements already described in the blood smears. Many of the immature lymphoblasts exhibit mitotic figures, despite the crude method in which the clot was obtained postmortem. Examination of these sections confirms the findings in the smears, with the added advantage of several staining methods. The nuclei correspond to those of the tumor cells to be described in detail later on. The binucleated forms and the shadows are found here also and identified with those of the smears.

Thrombus from Inferior Cava. This resembles ordinary thrombus and is composed of the usual elements, with a marginal zone made up almost entirely of the lymphoid cells.

Walls of Inferior Cava. The walls of the vein are densely infiltrated with tumor cells, which have broken them up into strands of necrotic fibrous tissue, undergoing hyaline degeneration. The tumor cells penetrate the intima, where they are found growing around the margin of the thrombus that has formed at that point. They resemble lymphoblasts to a striking degree and have a delicate reticulum growing all about them in the venous wall and the loose adventitial tissue surrounding it. Many pigmented phagocytes lie near them.

Kidney. There is fibrous obliteration of many of the glomeruli, most of which show thickening of their capillary tufts with an increase in the number of their nuclei. The capillaries contain many leukemic cells, some in mitosis. There is some degeneration of the tubular epithelium, with dilatation of the lumina and the formation of hyaline casts. The interesting feature, however, is the presence of large fields of tumor tissue in the cortex, sometimes resembling infarcts in their outline and distribution. The cells

lie in a well-formed reticulum, too generous to have been borrowed from the surrounding kidney tissue (Fig. 4). The peripelvic connective tissue is replaced by thick sheets of the same new growth, which is proliferating rapidly, forming a rather dense reticulum, and infiltrating the renal tissue in its vicinity. There is a definite resemblance between this neoplastic tissue and that found in the thymic region.

Uterus. The myometrium exhibits a marked nuclear hyperplasia, which is also noted in the endometrium. The uterine tumors are seen to be leiomyomas with some hyaline degeneration.

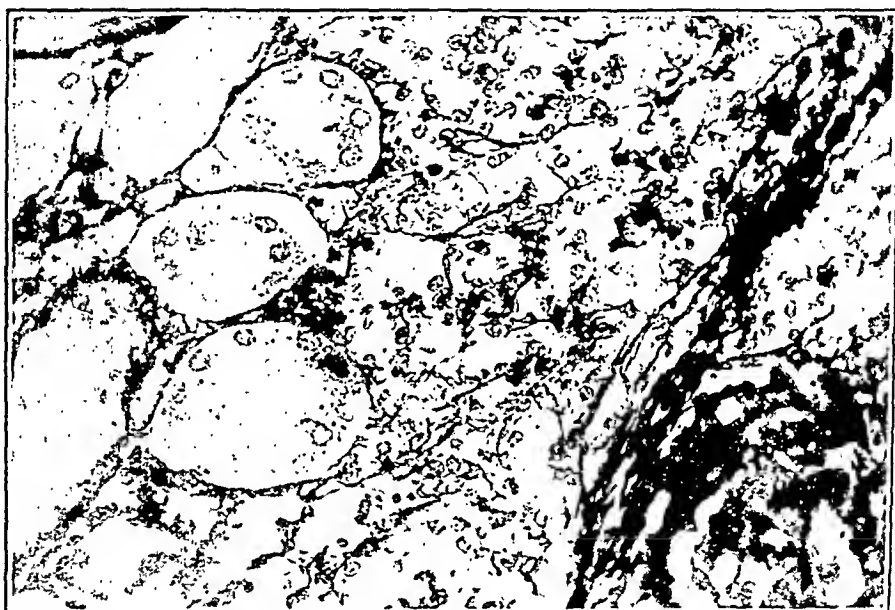


FIG. 4.—Kidney metastasis of the tumor, Bielschowsky-van Gieson, $\times 500$. The fine reticulum is apparently a product of the tumor. A fibrosed glomerulus is at one corner of the picture.

Vaginal Ulcer. This is a tumor metastasis, which has penetrated the vaginal wall and become ulcerated. It is identical in appearance with the tumor in the kidney, and is surmounted by a scab of leukocytes and debris. It differs materially from the sections removed at biopsy several weeks prior to the necropsy, in that they showed what appeared to be a chronic inflammatory process, with many immature lymphocytes infiltrating the tissue. Frank tumor, such as we now find at necropsy, was not yet present.

Examination of sections from the pancreas, adrenal, and thyroid shows these to be essentially normal, except for slight increase in the colloid content of the latter.

Detailed Description of the Tumor. *Thymic Growth.* The sections from the primary tumor show it to be composed of spheroidal or ovoid cells (Fig. 5) lying in a stroma, or reticular matrix composed of very coarse fibrils which vary from relatively fine and

straight, deep black in silver impregnations, to relatively coarse, waving and collagenous. The coarser the fibers, the more they tend to stain with acid fuchsin, or to take the purplish color in the silver-gold impregnation: the finer they are, the blacker (Fig. 6).

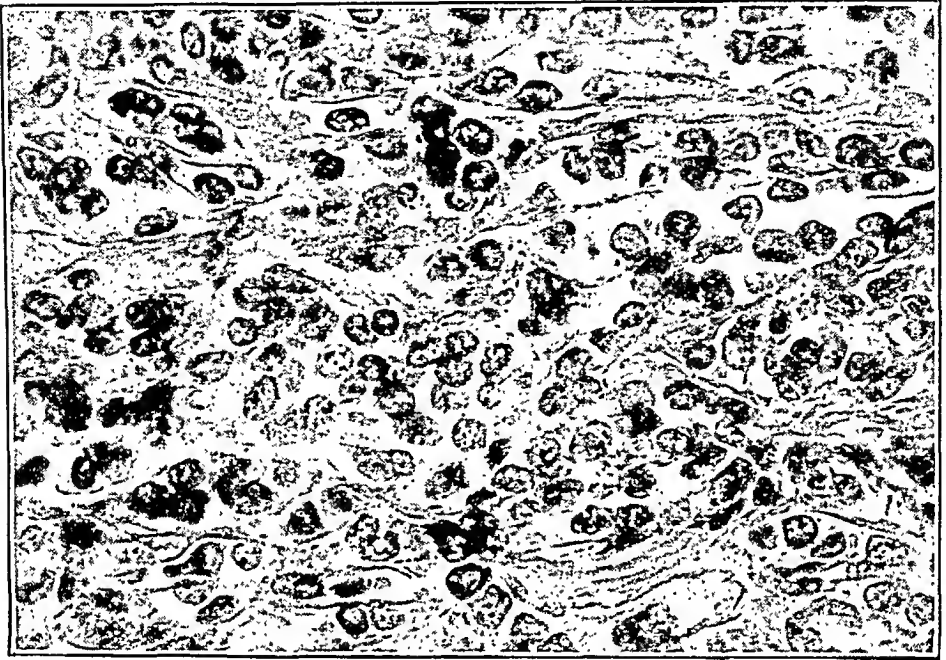


FIG. 5.—Thymic tumor, Mallory's phosphotungstic acid hematoxylin, $\times 1000$. Fibrous matrix of tumor well shown.

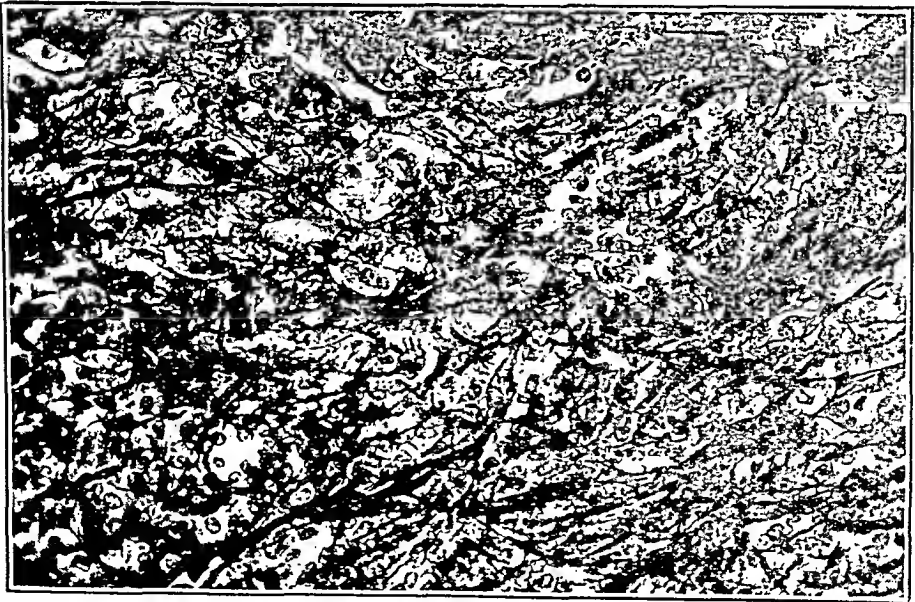


FIG. 6.—Thymic tumor, Bielschowsky-van Gieson, $\times 500$. The extremely dense reticulum is well shown and the coarseness of its fibrils very evident. Note that this plate is neither overexposed nor is the section overstained. The nuclei of the cells prove this.

Type Cells. These measure 5.5μ on the average, varying from 2.5μ to 8μ in diameter. In the latter case they are elongated and have a cross measurement of 5.5μ . There are occasional very much elongated cells 13.5μ by 6.75μ in size, usually occupying spaces in the denser reticulum. They may be tumor cells, or altered reticulum cells.

Nuclei. The nuclei are vesicular, rounded or ovoid, with a distinct nucleolus; the latter may be wanting, however, and two or three coarse karyosomes may be found in the delicate chromatin network. The latter usually shows thickenings similar to those seen in lymphoblasts. The nucleus occupies much of the entire cell and possesses a delicate, clean-cut limiting membrane.

Cytoplasm. This is very scanty as a rule, and is in the form of rounded or somewhat angular projections at the periphery of the nucleus, or as a trailing pseudopod. It may be almost wanting, so far as can be seen. It stains faintly violet with Giemsa's stain, deep red with eosin-hematoxylin, yellow in van Gieson sections, and faintly blue with phosphotungstic acid hematoxylin. Thus the cells may be spheroidal, elongated or ovoid when compressed, or even squash-shaped or irregular.

Mitoses. There are innumerable, very regular mitotic figures, quite free from asymmetry, which are found everywhere in the tumor and even in the blood stream and smears.

Stroma. Largely composed of coarse collagen fibers, it shows a background of finer reticulum. In the younger portions of the tumor the latter predominates, but even so, it is coarser than the usual lymphoid reticulum.

Metastases. These differ from the primary tumor only in the matter of their reticulum which is finer and less apt to be associated with collagen fibrils; and the fact that the cells do not stain as deeply nor average as large as those in the thymic region. Those in the blood stream are, so far as can be seen, morphologically identical with the cells of the primary growth and metastases.

This is particularly true of the Giemsa sections.

Discussion of the Pathological Aspects of the Case. Since publishing the last case of thymoma (Foot and Harrington, 1923) the writer has been unable to find any others listed in the Quarterly Cumulative Index. It is, therefore, unnecessary to discuss the subject from the standpoint of other writers, as this was done in the paper just mentioned and in its predecessor (Foot, 1920). In this particular case, we are confronted with two neoplastic processes: A malignant thymoma, with metastasis to the kidneys, inferior cava, vaginal fornix, and tonsil; and an acute lymphoid leukemia, in which the circulating blood and the lymphoid pulp of nodes and spleen are flooded with unripe lymphoblasts. These are so similar to the type cells of the thymic tumor that the question at once arises: Are we dealing with an outbreak of cells of thymic origin, through

a metastasis in the wall of a large vein, into the blood stream; or with a true lymphoid leukemia?

The answer to this question is the most important part of the pathological section of this article. Here, again, we collide with the old discussion as to the origin of the thymic "lymphocytes." The arguments for and against their being of mesenchymal, rather than of epiblastic origin, have been discussed in the 1920 paper on page 11. Briefly stated: Dantchakoff, Hammar, Maximow, and more recently A. Pappenheimer, believe that lymphocytes and lymphoblasts infiltrate the cortex of the developing thymus, ultimately filling it out completely. Bell, Prenant, Schridde, and Ewing, among other writers, adhere to the belief that these cells, although they closely resemble lymphocytes, are nevertheless different and represent descendents of epiblastic thymic reticulum cells. The case now under discussion certainly shakes one's faith in the latter theory. There is a blood-picture of acute lymphoid leukemia, with the type cells all definitely lymphoblastic.* Whence do they come? Upon examining the lymph nodes, tonsils, spleen and liver, we find instead of lymphoid hyperplasia, a hypoplasia of the lymphocytopoietic apparatus; the "germinal centers" are inconspicuous, there is no intensification of the lymph follicles, the splenic corpuscles are noticeably small and vaguely defined, and the lymphoid apparatus of the liver and lung are equally inconspicuous. All of the lymphoid organs show a diffuse distribution of rapidly multiplying lymphoblasts in the meshes of the pulp, but this is also true of the circulating blood. No definite tumor of lymphoid character is found, aside from the thymic neoplasm and its metastases. Here the cells of the tumor bear a striking resemblance to those in the circulating blood.

Therefore, everything points to the thymic tumor as the origin of the circulating lymphoblasts. The conclusion is obvious: Either we are dealing with a malignant thymoma which is throwing into the circulation cells morphologically identical with lymphoblasts, but not true lymphoblasts because of their epiblastic origin; or, second, with a malignant thymoma accompanied by an acute lymphoid leukemia, the origin of which is not traceable to the lymphoid tissue; or, third, with a malignant thymoma composed of true lymphoblasts, and hence a form of lymphosarcoma which is casting tumor cells into the circulation and producing a lymphoid leukemia. In the first case we must suppose that all lymphoid leukemias are not necessarily of lymphoid origin, but may arise in the thymus; in the second we have a lymphoid leukemia developing *ex vacuo*; in the third we must admit the mesenchymal origin of the thymic cortex. Which is the most logical of these conclusions?

* Dr. Ewing, who has seen sections from this case, admits this point in a letter to the writer.

Whilst it would seem that the third is, there are two facts against it: The lymph nodes are not usually involved in these thymic tumors and are often incorporated in them *in toto*, without material alteration in their histological make-up; and the reticulum formed by the thymoma is straighter and coarser, and apt to be more collagenous than that seen in true lymphosarcoma. By their long residence in the thymic cortex, however, the lymphocytes may have undergone a change in their physiology, which might influence their reaction to neoplastic stimuli. It would be more difficult to explain the lymphoid leukemia in this case, as a phenomenon independent of the thymic tumor, than it would to account for the two objections just stated as opposed to the theory that it depends directly upon the thymic tumor. We are, therefore, probably dealing with a lymphosarcoma of the thymic cortex, or small-celled malignant thymoma, and with a lymphoid leukemia directly connected with it and originating in the thymic cortex. Furthermore, we can adduce the generalization that all of the thymic sarcomata of definitely lymphoid type are, indeed, lymphosarcomas and therefore genetically unrelated to the other, or epiblastic type of malignant thymoma. This case is also useful as supporting the theory of the mesenchymal origin of the lymphoid elements of the thymic cortex, and hence it is a contribution to normal histology and embryology.

Summary. 1. The patient has a malignant thymoma of the small-celled type.

2. She has an acute lymphatic leukemia.

3. It is more reasonable to explain the latter as a direct result and derivative of the former, than as an independent process.

4. Therefore this form of thymoma is a true lymphosarcoma, although differing in some respects from the usual types of that tumor.

5. There are peculiar epithelial inclusions in the retroperitoneal lymph nodes, which are probably derived from displaced mesonephric tissue.

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THE HEREDITY FACTOR IN PERNICIOUS ANEMIA.

BY E. MEULENGRACHT,

COPENHAGEN.

(From the Bispebjerg Hospital, Copenhagen.)

THE advance of knowledge brought about by modern experimental research has opened our eyes to the fact that the causes leading to many diseases are so intimately connected with hereditary factors that their pathogenesis can only be understood in the light of these factors. It seems appropriate to review some points of importance in this connection, choosing as a particular illustration pernicious anemia.

The causes leading to the development of a disease lie partly in the individual himself and partly in external factors. Although these two sets of causes can often be clearly defined, much confusion has been caused by the use of words such as, for instance, constitution or similar vague terminology. Different schools have ascribed different meanings to this term, so that its use tends to a lack of discrimination between, on the one hand, the influence of heredity and, on the other, the influence of external conditions. We would do better to adopt in medicine the terminology as well as the teachings of the science of heredity. W. Johannsen, of Copenhagen, has coined the terms: The genotype, the external conditions and the phenotype.

The *genotype* of an individual signifies the basic peculiarities present in the fertilized egg, which determine the individual's possibilities in development.

The *external condition* are the external influences met with in life.

The *phenotype* signifies the personal characteristics of the individual resulting from the interaction of genotype and external conditions.

For every characteristic (or disease) we meet the following triad: The *genotype* in its interaction with the *external conditions* determining the characteristic (or disease).

Keeping this fact in mind, it is evident that the unravelling of the pathogenesis of a disease necessitates an inquiry first into any peculiarities of the genotype and secondly into any peculiarities of the external conditions. Genotype and external conditions together determine the manifestations of the disease.

I. The Genotype. Observation on the heredity occurrence of pernicious anemia.

Turning to the particular subject in hand, pernicious anemia, we may first consider the genotype, what we know about it and what we may possibly learn from special investigation. The genotype represents the hereditary factors and these are passed from genera-

tion to generation, according to the laws of heredity. Our first question concerning pernicious anemia is naturally whether there is evidence of heredity in the incidence of this disease. It is only recently that this question has attracted more than a casual interest. A historical consideration of the evidence is important, since it shows a development of our ideas, which is typical for many other diseases.

Klein,¹⁵ in 1891, that is, twenty years after Biermer⁴ had described the disease, casually mentioned that he had seen the disease in 3 brothers and sisters. Some years later Byron Bramwell described a family in which 7 individuals in two generations had suffered from pernicious anemia. In the following years a series of such reports were made, generally describing 2 or 3 cases in the same family either among brothers and sisters or in successive generations among the lineal or near collateral descendants (Caccini,⁷ Schauman,²²⁻²⁷ Gulland,¹³ Cabot,⁶ Gilbert and Weil,¹⁰ Patek,²⁰ Willson,²⁹ Andrée,¹ Bartlett² and Roth²¹).

Matthes¹⁷ reported that he had observed hereditary pernicious anemia several times, and Gulland and Goodall¹³ reported on the basis of their personal experience with some 500 cases, that pernicious anemia not infrequently occurs in several members of the same family; in one family they observed 5 cases. For the most part this hereditary incidence was mentioned incidentally and more or less as a curiosity, and no special point was made of its importance in the nosography of the disease.

To give heredity a foremost place in the etiology of pernicious anemia two things were necessary: (1) A man who should recognize the importance of heredity in this disease, and should systematically investigate it from that standpoint throughout several years; (2) a new point of view in pathology. The man was the late Finnish hematologist, Ossian Schauman, and the pathological movement was so-called "constitutional pathology," or doctrine of endogenous cause of disease. In the year 1900 Schauman had reported a few apparently hereditary cases of bothriocephalus anemia, but in 1918 his material had grown to include twenty-four families in which there was noted an hereditary occurrence of either idiopathic pernicious anemia or of pernicious anemia due to bothriocephalus, or of both of these, in the same family. From these observations Schauman was led to believe that the hereditary incidence of pernicious anemia was a frequent phenomenon. The hereditary occurrence of pernicious anemia is now recognized to be not merely an occasional curiosity but a frequent and noteworthy fact. More recent publications have come from the hands of Levine and Ladd,¹⁶ Meulengracht,¹⁸ Gram,¹² v. Decastello,⁸ Mustelin¹⁹ and Gilford.¹¹

Thus there already exists sufficient material to indicate that this disease may occur with an hereditary incidence, and this must mean that special elements in the genotype play an important role

in its etiology. This statement assumes, however, that the occurrence in certain families is due to true heredity and is not caused by a common external cause. This assumption is supported by the observation that the cases have occurred only in members of the families concerned and not in other members of their households. Furthermore endemic groupings of the disease are not known, and the several diseased members of a family have often lived in different localities and at different periods.

The next problem is whether we can learn anything concerning the peculiarities of the genotype which determine the etiology of pernicious anemia?

The problem of investigating heredity in human pathology is far more difficult than is that of the research worker who employs cross-breeding as his principal method. Thus Mendel investigated the factors underlying different properties of heredity in plants by systematic cross-breeding between different varieties. Such deliberate experimentation is, of course, not available in human pathology, where we are restricted to the results of spontaneous cross-breeding. The material which is furnished under natural condition is in many ways most unfavorable for analysis. For instance interbreeding of brothers and sisters, which furnished some of the most valuable experimental results, does not occur in the human race. Furthermore, the average interval between successive human generations is about thirty years, so that a single person at most can hope to observe only two or three generations, while the experimental worker may see the same or a larger number with one year. Finally the human progeny in each generation is generally much less numerous than that employed in experimental studies. These among other conditions constitute a serious handicap to investigations on the influence of heredity in human pathology.

Nevertheless there are two methods available for this purpose, namely, the analysis of casuistics and the method of statistical summation.

The Analysis of Casuistics. Using this method, we endeavor to follow the hereditary manifestations of disease through a series of generations and special families are chosen either because the disease for some reason or other has been richly represented in the family, or because special conditions have favored an investigation. The method involves both collecting the data and attempting to interpret it.

In collecting the material we meet with: (1) A genealogical problem in the determination of the family relationships; this may be neglected in this discussion. (2) A medical problem in the recognition of the disease which is a considerably more difficult matter. With most diseases the determination of the existence or absence of the disease among the members of the family becomes insurmountably difficult as soon as we try to pass beyond the

immediate family circle. The family history becomes more and more vague the further we go. The diagnosis of the condition may be fairly easy if there are certain striking features characteristic of the disease. However, if the symptoms are less obvious, or if they may be confused with those of other diseases, the possibility of getting a reliable family history is very slight. In many instances it may even happen that the recognition of the disease is difficult by direct examination, and requires special and complicated apparatus. After collecting the history of a series of generations of carefully investigated individuals, the interpretation of the material depends upon a comparison between the incidence of the disease in the family and that demanded by the laws of heredity as established by experimental research, assuming that these laws are valid for human beings. Frequently it is possible thus to determine the type of inheritance involved and to get a more or less clear conception of the peculiarities of the genes (inheritance factors) which carry the disease. This method includes an investigation of other peculiarities or diseases occurring in the affected individuals which might possibly be due to the same genes in identical or different combinations. Most of our knowledge of heredity in human pathology has been arrived at by such analysis of casuistics. It is inevitable, however, that in selecting the families that show numerous instances of the disease under study we are guilty of a one-sided selection. The frequent occurrence of the disease may be due to a favorable cross-breeding, but it may also be mere chance. The method has been severely criticized, therefore, from a statistical standpoint, and an attempt has been made to find a sounder statistical basis for analysis in the so-called method of statistical summation.

The Method of Statistical Summation. In this method one restricts oneself to a single generation and investigates the numerical relations of diseased and of sound progeny resulting from those crossings which could give rise to the disease. Because of the paucity of the human progeny, however, it is necessary to deal with the average values obtained by a summation of the healthy and diseased progeny in a series of families. From the resulting figures the attempt is made to draw conclusions as to the nature of the genes in question. The necessity for such a summation may be appreciated from Fig. 1, which gives the probable distribution of disease in 16 two-children marriages, where both parents have a recessive hereditary characteristic. In the offspring of 100 individuals the result would be one-quarter diseased and three-fourths apparently healthy, but in small progenies each with 2 children, the results are entirely a matter of chance. The same difficulty of course would apply even to greatly larger progenies, but the error increases with a diminishing number of children.

In order to obtain an average value, as many progenies as possible are studied. In practice, however, we meet at once with difficulties.

We should study all progenies capable of producing the disease, so as to avoid a one-sided selection. But our selection discovers only the progenies in which the disease occurs, not those in which it might occur but is missing by chance. These "positive" progenies will give us false pictures; for example, in Fig. 1, we can find the progenies which show diseased members, but not those showing only healthy persons, since these latter ones cannot be distinguished from any ordinary progeny. This seemingly insurmountable difficulty can nevertheless be overcome by the so-called kin-incidence* method ("probandemethode") of W. Weinberg. The principle of this method is an analysis of the progenies that show the disease, therefore a one-sided material. In the analysis a special form of statistical calculation is used in which one considers the kin-incidence of the disease for each individual, that is, the number of diseased and the number of healthy brothers and sisters for each diseased individual. This method gives the same numerical proportions as an analysis of both the positive and negative progenies.

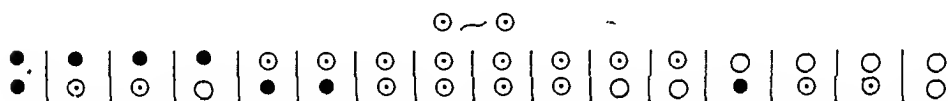


FIG. 1.—The probable distribution of diseased and healthy offspring in 16 two-children marriages when both parents possess a recessive disease factor. ●, diseased; ○, phenotype healthy, but recessive disease factor present; ○, healthy.

The proof of the validity of this method cannot be given here, but as an instance we will consider the progenies shown in Fig. 1. We consider simply the seven progenies containing diseased members. A simple summation would give the quite misleading ratio: 8 diseased to 6 health individuals. If, on the other hand, we count the kin-incidence of the disease for each diseased individual we get 2 diseased and 6 healthy kin. The ratio then is 1 diseased to 3 healthy or the same as in the total (ideal) material. This method thus allows us to calculate the average ratio between diseased and healthy individuals. This is then compared with the Mendelian ideal proportions for the ratio of variants in different types of crossings. The ratio observed is compared with the different possible ideal ratios to see which it resembles. Often the analysis of casuistics suggests a certain type of heredity and a certain number of significant genes, and one may there make use of the method of statistical summation for a numerical confirmation.

Here, however, the difficulties are not at an end, for an assumption which underlies the statistical method is that the incidence of the disease corresponds with the presence of the specific genes. Several possibilities may invalidate this fundamental assumption; for example, a tendency for the disease to appear only late in life,

* Incidence in a progeny of brothers and sisters.

or the development of the disease only in association with special external conditions. If a disease appears only late in life or requires special external conditions for its development, the frequency of its occurrence will always be less than the frequency with which its specific genes are present.

Technically this is called a disturbance of the ideal incidence; it is stated that the actual incidence is less than the ideal incidence. Therefore, the statistical method must be used with the greatest caution and, as a rule, demand better material and more knowledge of human pathology than we yet possess.

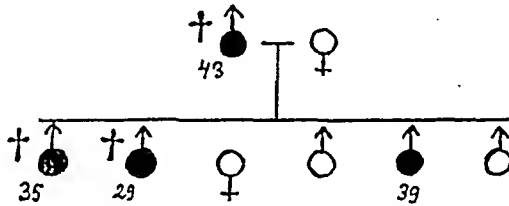


FIG. 2.—Pernicious anemia in a family observed by Bartlett (1913). ●, diseased; ○, healthy; ♂, male; ♀, female; +, dead.

The Analysis of Casuistics as Applied to Pernicious Anemia. The results of this method have thus far not been striking. From among the studies that have been published we may select the family described by Bartlett (Fig. 2). A father and 3 of his 6 children suffered from pernicious anemia. A survey of the literature yields a large number of similar observations, where the observer has recorded his material merely to suggest that an hereditary factor

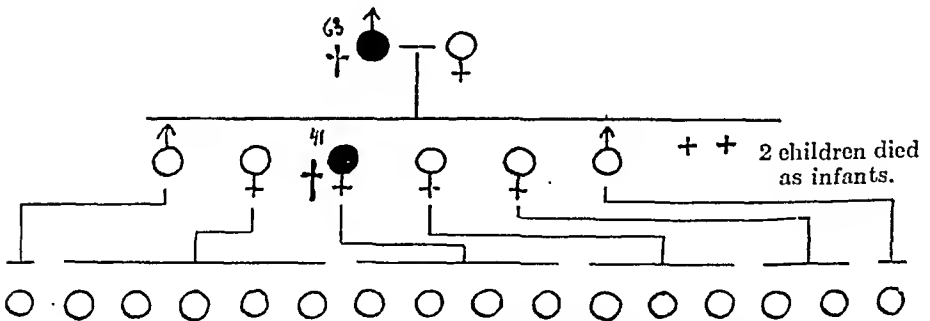


FIG. 3.—Pernicious anemia in a family observed by the author.

plays a role. These reports deal, as a rule, with cases in one or two generations, in lineal or collateral descendants. As a rule, no further investigation of the family has been carried out. The difficulty of developing such a family history is well illustrated by a family (Fig. 3) observed by the author. A father and daughter had died from pernicious anemia, and it was desired to find out whether other cases had occurred in the family. When one attempts to elicit the history of earlier generations, even if the ancestors

are known, it is impossible to ascertain the presence of the disease. The diagnosis is difficult and the recognition of the disease dates only from recent years, so that at most we can go only to the previous generation. Among the descendants we are balked by the fact that possibly only after twenty or thirty years will the youngest generation have reached the age at which the disease generally makes its appearance. The same applies to another family (Fig. 4) observed by the author. Four brothers and

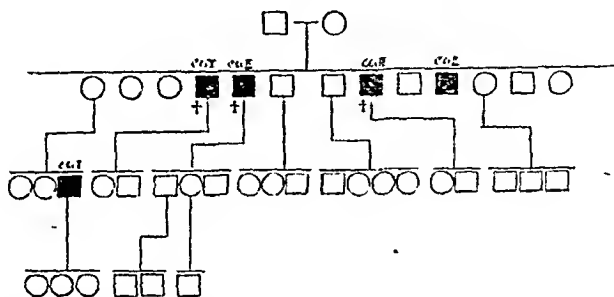


FIG. 4.—Pernicious anemia in another family observed by the author. □, males; ○, females.

a nephew showed the disease. Concerning the parents of these 4 brothers the information is vague, and in the later generation we find only children who have not yet reached the age of manifestation. Only one family history, which has been published by Mustelin (Fig. 5), describes the disease in three successive generations of lineal descendants. This, in connection with certain other observations, led Mustelin to offer the hypothesis, that pernicious anemia is a *dominant property depending on a single gene*. Lineal inheritance through several successive generations is one of

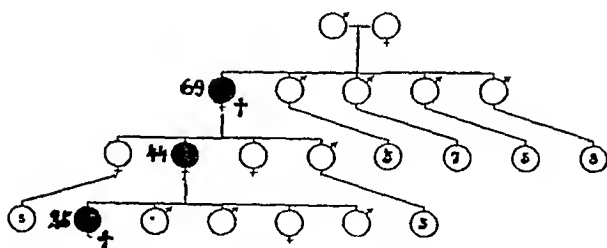


FIG. 5.—Pernicious anemia in a family observed by Mustelin (1922).

the characteristics of a dominant property. A family history such as this undoubtedly supports this hypothesis; at least simple recessive inheritance is made extremely improbable since this would require that three lineal descendants in successive generations should have married recessive heterozygotes, which, owing to the rarity of the disease, would be very unlikely. With our present knowledge we can only say that there is nothing to exclude the hypothesis of Mustelin.

Films showed a typical megalocytic picture, and the average diameter of the corpuscles was increased to 8.8μ . There was a leukopenia, bilirubinemia and urobilinuria, a slight platelet deficiency, a gastric achylia and the characteristic periodic glossitis. In spite of the 98 per cent hemoglobin the patient had a classical pernicious anemia, which was fully confirmed by subsequent events. This patient was discovered in the well-known initial stage of the disease, but except for a painstaking examination would have been classified as healthy.

A further investigation of this family shows the interesting fact that not less than 6 individuals beside the 3 cases of frank pernicious anemia suffered from gastric achylia (shaded in the diagram): Of these 6, 4 (marked $\times\times$ in the diagram) also had the typical glossitis. This important symptom, characteristic of both the prodromal and of the fully developed cases, has too often been neglected. Concerning 1 of these 4 achylia-glossitis cases, it is recorded that a later examination a few years before his death showed a slight anemia of megalocytic type, so that the examining specialist suspected an incipient pernicious anemia. The question arises: Which of these members shall we classify as healthy and which as diseased? The frank pernicious anemias are clear enough, but what about the 6 others? Are they incipient cases, which would have developed into frank pernicious anemia, are they "larval" cases arrested at a prodromal stage, or are they cases with vicarious symptoms arising from the same genes, possibly in other combinations?

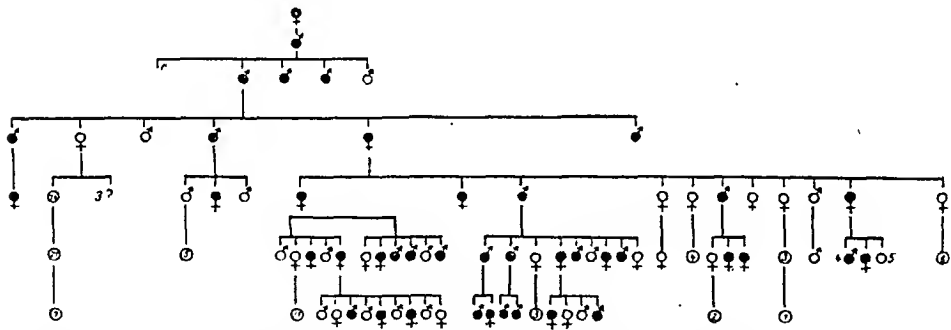


FIG. 7.—Brachydactylia in a family observed by Drinkwater (1908). ●, abnormal; ○, normal.

The answer to these questions will probably eventually be given by further observations of this and other similar families. The finding of achylia and glossitis in families with pernicious anemia may be of great significance in studying the pathogenesis of the disease. At present we must admit that the distinction between the presence and absence of the disease in this, as in other maladies, is at times uncertain.

The late appearance of pernicious anemia, the difficulties of diagnosis and the possible influence of external conditions make it

impossible to get family histories as adequate as in diseases which are manifest at birth. For example, Fig. 7 (after Drinkwater) shows a family with brachydactylia which is an hereditary condition due to a single dominant gene. Contrasted with this material, our data relating to pernicious anemia looks most unsatisfactory, but nevertheless the importance of the question makes the collection of further material imperative.

The Method of Statistical Summation Applied to Pernicious Anemia. As already stated, this method consists in collecting data concerning one generation of families and analyzing them by Weinberg's "kin-incidence" method which would give the average incidence of the disease which may be compared with the Mendelian ideal proportions. A supply of such systematic data does not as yet exist for pernicious anemia, but sooner or later it will be available. However, it is well at the start to appreciate the difficulties in interpretation which will be met with and which make it doubtful whether we can ever secure definite results by these methods.

The chief difficulty, as has already been pointed out, lies in the late age of manifestation of the disease, the influence of which can be aptly illustrated by two instances (Fig. 8).

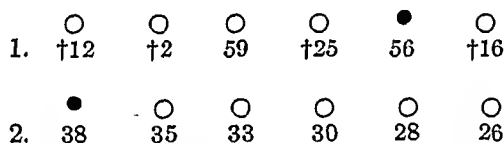


FIG. 8.—Instances of two progenies of brothers and sisters chosen to show the difficulties of statistical treatment.

We have two progenies of brothers and sisters. In the first 1 is suffering from pernicious anemia, but 4 of the remaining 5 died so early in life (twelve, two, twenty-five and sixteen years old) that it is impossible to state whether some of them would have developed pernicious anemia later in life, in which case they would not of course have had to be recorded as healthy.

In the second progeny, also, the oldest is suffering from pernicious anemia, while the 5 younger members are still at an age where the disease only very rarely develops. At the moment one must record 5 healthy members and 1 diseased, but some of the former may later develop the disease.

In our determination of the ratio between healthy and affected members, the number of the apparently diseased will always lag behind that expressing the presence of the actual specific hereditary factor underlying the disease.

The observed incidence will, on account of this late term of manifestation, be very much lower than the ideal incidence. Therefore conclusions from the observed incidence as to the type of heredity must be qualified. This error might be eliminated if we

could calculate the errors due to too early death and too early observation. In a recent work by Bauer and Aschner, these authors have suggested a method which in their opinion allows a calculation of this error. Their method is called the compensation method, and is designed to be used with the "kin-incidence" method of Weinberg. Apparently the authors contend that their method could be applied to pernicious anemia, since they offer it for use in diseases that appear late in life. The method is very complicated, and entails elaborate statistical calculation. Without claiming to be a judge of statistical calculus, the present author believes the method to be erroneous and to be based on false assumptions.

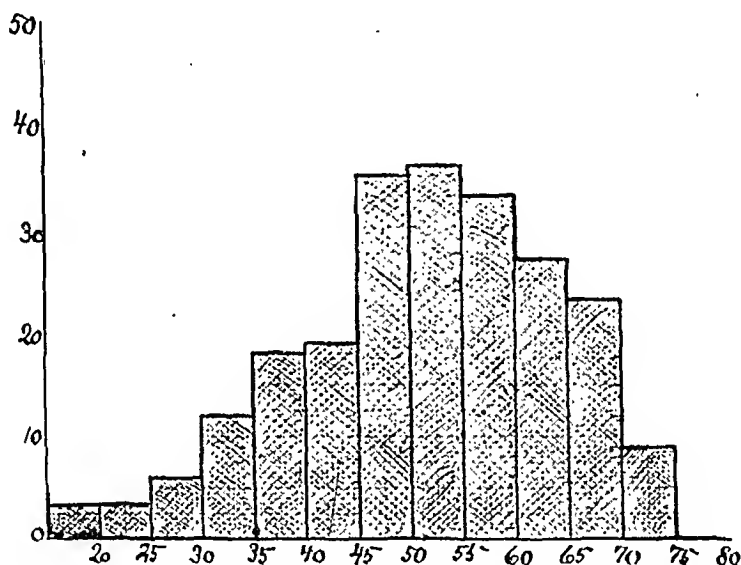


FIG. 9.—Distribution of Eason's 220 pernicious anemia cases between the various age classes. Ordinate, number of cases in each class; abscissa, age of manifestation. *Fig. 9*

Pernicious anemia is distinctly a disease of later life. A diagram constructed by using Eason's 220 cases shows the frequency of manifestation at various ages (Fig. 9). The greatest incidence is found at between forty-five and sixty-five years, with a rapid decrease after the sixty-fifth year. This decrease, however, is not a true one, but arises from the higher mortality and, consequently, lower number of individuals at the higher ages. On account of this decrease in the number of elderly persons, any characteristic—in our case pernicious anemia—must have fewer examples in old age. If, to avoid this fallacy, we construct a diagram of the same material, arranged in relation to the total number of individuals of each age in the total population (Fig. 10), we get a steady rise. Pernicious anemia can thus be shown to be distinctly a disease of old age, with a period of manifestation which is not ended at the age when death on the average occurs.

Now the compensation method of Bauer and Aschner previously

mentioned rests on the false assumption that the probability of manifestation decreases in old age. This is true in the case of diseases such as dementia precox or Huntington's chorea (Fig. 11), which appear early in life, and in this and similar types of disease it is possible by intricate probability calculations to arrive at a figure expressing the number of apparently healthy persons who would have shown the disease had they lived long enough. But in diseases which, like pernicious anemia, become more likely with age, the apparent decrease in old age is a fallacy. All things considered, therefore, one must not expect too much of the method of statistical summation applied to pernicious anemia. The problem of pernicious anemia, on the whole, is hardly ripe for the finer statistical methods.

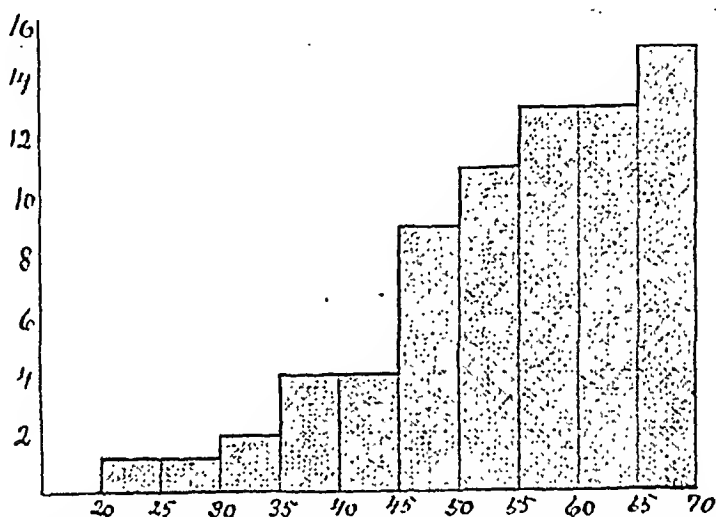


FIG. 10.—Eason's material re-arranged to show frequency in relation to total number of individuals at same age. Ordinate, cases per 100,000 individuals of same age; abscissa, age of manifestation.

One may ask in general: How often is heredity apparent in pernicious anemia? This naturally is not the biologically crucial point, but it has some importance, for many clinicians consider it a very rare occurrence. We are forced to admit that in the majority of cases heredity cannot be traced, at least, among the closer relatives. However, the frequency with which heredity can be found certainly increases markedly when attention is directed toward this point, a phenomenon not without parallel in other clinical investigations. The more systematic the search that is conducted and the more thoroughly one examines the family history, the more often are instances of possible heredity observed. As a striking instance of this the family charted in Fig. 4 can be taken. For six years the author had attended 1 of the members before he learned that 4 individuals closely related were suffering or had suffered from pernicious anemia. After his interest in the subject

had been awakened by this observation he was able to find several other families with multiple occurrence of the disease. Those who are not especially interested will fail to make such observation, and any figures relating to the frequency of apparent heredity will be minimal figures without such search. This consideration also applied to the recent figures of Levine and Ladd, who in 143 cases of pernicious anemia 9 times found other cases in the immediate family (parents, brothers, sisters and children), that is, in 6 to 7 per cent of the material. This certainly is a minimal figure, since the investigation does not seem to have been very energetic, and only encompassed a very narrow range of relatives. Even so, however, this percentage is too high to be mere coincidence; the disease is so rare that a similar investigation of the family histories of the same number of control individuals gave the author zero incidence as a result.

On the other hand, 6 to 7 per cent seems extremely low if one accepts the admittedly highly hypothetical assumption that pernicious anemia is due to a dominant single cure. The ideal proportions then would require a much higher percentage.

The problem is whether this enormous difference can be explained entirely by the late age of manifestation, difficulties of diagnosis, etc., or whether we must assume that special external conditions, not always present, are necessary for the development of the disease. This certainly is a fundamental question. Although upon the assumption just referred to the evidence of heredity in pernicious anemia might be expected to be apparent in nearly every family with the disease, the rarity of such observations may be due entirely to the late age of appearance, since the frequency of manifestation (Fig. 10) steadily increases as long as the duration of human life allows us to follow it.

It is interesting to make a comparison with another disease—diabetes—which has a correspondingly late period of manifestation (Fig. 2) and to which a similar type of heredity has been ascribed. It seems as if medical opinion is more willing to admit that this is a disease founded on some alteration of the genotype and that it does not require special rare external conditions for its development. One of the best investigations of diabetes has been made by Joslin, who in 21 per cent of his 1167 cases found evidence of heredity within a range encompassing parents, brothers and sisters, children, uncles, aunts and cousins. In the majority of cases (79 per cent) heredity was not apparent, but even the figure 21 per cent is much higher than that found in pernicious anemia (6 to 7 per cent). Now diabetes is so frequent a malady that it will, according to Joslin, be found in the families of 5 per cent of a similar number of non-diabetic controls. If then 5 per cent is subtracted we get 16 per cent. Furthermore, the investigated range of relationship is much greater than that which Levine and

Ladd applied to their pernicious anemia material. The author is inclined to believe that a correction for this difference would nearly halve the figure, so that one would approach the 6 to 7 per cent found in pernicious anemia, and even if this were not quite true the age of manifestation of pernicious anemia tends to fall somewhat later than that of diabetes, so that this would explain a slight further discrepancy between the results.

If one will admit that the low percentage of apparent heredity in diabetes is due to late manifestation and not to lack of special external conditions, the same explanation could be applied by analogy to the low percentage in pernicious anemia.

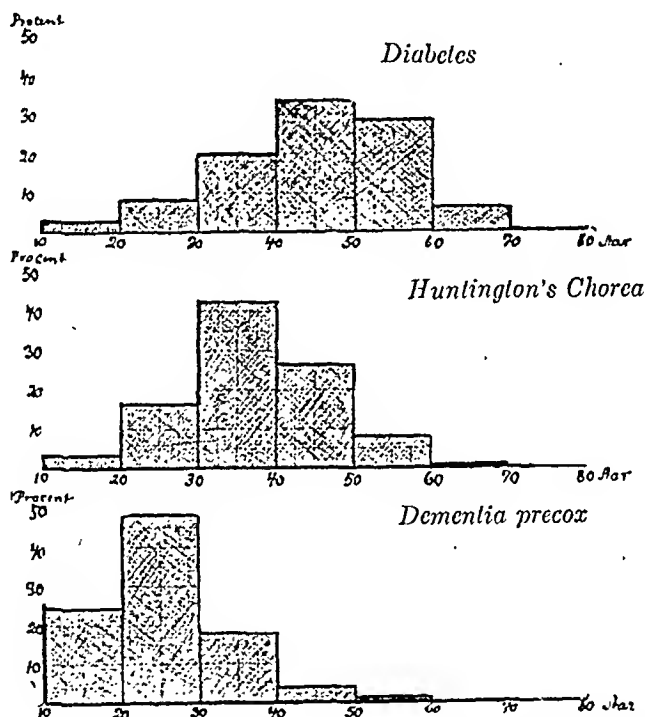


FIG. 11.—Distribution of diabetes (v. Noorden), Huntington's chorea (Entres) and dementia precox (Kraepelin) between the various age classes. Ordinate, percentage number of cases; abscissa, age of manifestation.

We wish here to stress strongly the point that the apparent isolation of cases of a disease within a certain range of blood relationship does not constitute an argument against the hereditary nature of the disease. It is often said that the etiology role of heredity in some disease cannot be of great importance, because the evidence of heredity so rarely appears. This is a quite unwarranted statement, inasmuch as the rarity of apparent heredity to example may be due to late age of manifestation or to the rarity of the formation of the necessary gene combination.

On the whole our knowledge of the inheritance of pernicious anemia is rather scanty. We are hampered by the late age of

manifestation, especially when we try to calculate whether this alone will account for the low actual proportions of hereditary incidence or whether we must assume in addition the presence of special external conditions. If such a calculation were possible it might give us valuable information on the etiological role of external conditions.

Now let us turn our attention directly to the external conditions reviewing what clinical experience has taught us about the role played by certain external conditions in the development of the disease.

External Conditions Provoking Pernicious Anemia. The most obvious fact in this connection is the pernicious anemia associated with bothriocephalus. In a certain number of bothriocephalus hosts there develops a classical megalocytic anemia with typical organic changes (glossitis, etc.). In most of these cases (according to Schauman and Levander in 85 per cent) the fully developed anemia is accompanied by gastric achylia. If the parasite is expelled by a vermifuge one of three results may follow: Either the patient is permanently cured or, much more rarely, a remission sets in, followed by a relapse of apparently idiopathic pernicious anemia, or thirdly (in 12 out of Schauman's 72 patients) the expulsion leads to no improvement at all and a progressing deterioration and death follows.

It cannot be too much emphasized that the bothriocephalus anemia occurs only in a very small minority of the hosts. In Finland, where one-third of the population are infested with this parasite, it is estimated that only one pro mille of the carriers contract pernicious anemia. Also tænia tapeworms have been shown to provoke pernicious anemia, but only extremely rarely.

In a smaller series of observations pernicious anemia has been seen to develop in individuals suffering from old cicatricial constrictions of the small intestine (with stagnation of the contents above the constriction). This seems, however, to happen only in a small proportion of the cases of intestinal stricture.

Lastly, there is the pernicious anemia of sprue. In the literature one finds described cases of Oriental sprue in which an anemia occurred, which, according to the examining hematologists, was of the classical pernicious type. This anemia is said to be cured when the sprue is improved by rational dietetic therapy (milk). As yet this anemia of sprue has not been sufficiently studied.

It is worth noting that all the above-named conditions (namely, bothriocephalus, tænia, intestinal constriction and sprue) have in common an involvement of the intestinal canal. This is not true of certain other conditions which are sometimes erroneously given as causes of pernicious anemia. It cannot be said that any valid connection has been established between syphilitic infection and pernicious anemia. The cases brought forward in the literature

may well have been coincidences, and no convincing therapeutic results of antisyphilitic treatment have been noted.

The so-called pernicious anemias of pregnancy vary both clinically and hematologically from genuine pernicious anemia, so that it is doubtful whether they belong to the same nosographic entity. More probably they represent a special type of toxic anemia.

These latter conditions therefore will be disregarded, or, at most, considered as a group of various external conditions which may possibly hasten and exacerbate the development of a pernicious anemia. There still remains the large main body of cases, in which no external causal conditions can be found; these are designated as idiopathic pernicious anemia, and in these the lack of facts has obliged us to take refuge in hypotheses.

The constancy of gastric achylia in these cases has attracted general attention, and there is a widespread view that pernicious anemia is a consequence of the preëxisting achylia. This explanation has been rejected by several authors, who think that the achylia is a collateral phenomenon, that is, one of the earliest and most characteristic prodromal symptoms, that it may be present for years before the onset of anemia and that it is found also in bothrioccephalus anemia, where it must be considered a result of the intoxication. According to the first view the achylia would represent a special condition favoring the development of pernicious anemia, while according to the second which is that of the author, it is to be considered only a symptom.

The conditions named above, intestinal parasites, intestinal constrictions and sprue, do not give us any idea of the pathogenetic agent, and we know nothing concerning its nature. The character of the disease has led to the following conclusions: It seems certain that we have to deal with a general intoxication, which in the later stages fatally affects the blood, and the blood-forming organs. It must not be forgotten that this intoxication affects more than the blood and bone-marrow, since a whole series of organs (tongue, peripheral nerves, central nervous system, heart, muscles, liver, kidneys and stomach) are both functionally and anatomically impaired. What causes are responsible for this intoxication we do not know, but they seem to be connected in some way with the digestive tract.

Experimental research upon this point has up to the present give us no conclusive results. *A priori* one would think that the bothrioccephalus anemia would furnish the best point of attack in this connection, because the anemia might be due to substances given off by the parasite. In spite of extensive work on this subject, no such toxic substances have been demonstrated with any certainty.

Therefore, a probable explanation seems to be that the bothrioccephalus acts not by secreting special toxic substances from its own body, but that its presence in the intestine serves to set at

work the same unknown factors that are active in the other forms of pernicious anemia. In all types of pernicious anemia we would have then to deal with the same intoxication. In favor of this view one can cite two important facts: (1) *Bothriocephalus* anemia may recur after successful expulsion of the worm and resemble then idiopathic pernicious anemia; (2) *bothriocephalus* anemia also tends to occur in certain families, sometimes alternating with idiopathic pernicious anemia; this would seem to indicate that both types are due to the same factors and to the same specific character of the genotype. The cures after expulsion of the parasite would then be considered only very marked and prolonged remissions.

From therapeutic results nothing can be concluded as to the nature of the assumed intoxication. The capricious remissions may be seen following all sorts of treatments.

The mode of action of any significant external conditions is still unknown, so that we cannot decide whether certain external conditions are necessary for the development of pernicious anemia or whether they only favor it.

Returning to the fundamental principle: The genotype in its reactions with the external conditions gives rise to any property (or disease) we may consider, whether our present knowledge of genotype and external conditions permits us to form any conception as to the relative importance of these two factors in the etiology of disease in general. First we will disregard our specific instance pernicious anemia, and inquire into the general applicability of the principle.

This principle as stated includes all transitions between two extremes. One extreme is that a property or disease is solely dependent on the genotype, the character of the external conditions being immaterial, so long as they permit life and development. An instance of this is found in the hereditary deformity, brachydactylia. The deformity appears whenever the peculiarity of the genotype is present whatever the external conditions may be.

The other extreme is represented when a disease or property is solely dependent on external conditions without being influenced by the genotype. As an instance we may take a burn; in this case the role of the genotype is only that of providing an individual who can be burned. As a general rule, we can say that the more a disease depends on the genotype, the more the influence of heredity will appear and the more its inheritance will follow the laws of the specific peculiarities of the genotype.

Likewise the more a disease follows some known law of heredity, that is, the more the actual incidence approaches the ideal incidence the more likely is it that special external conditions are either not necessary or if so are constantly present.

In the special case of pernicious anemia we have seen that certain factors in the genotype appear to be of importance and that some importance appears to attach to certain external conditions.

The problem then is whether one or the other of these two is absolutely necessary or are they only to be considered as favorable to the development of pernicious anemia, so that one or the other may be missing under certain circumstances.

Our present knowledge of both factors is too slight to allow our drawing final conclusions, therefore a discussion of the possibilities would hardly prove fruitful. The author intends merely to put forward an hypothesis that can explain the known facts: The disease requires for its development a specific hereditary peculiarity in the genotype. The external conditions that have been discussed, and possibly others of unknown character, will in the hereditarily disposed individuals cause an earlier appearance of the manifestation. The external conditions are not strictly necessary, but act by favoring the development of an unknown intoxication. Leaving this not unassailable hypothesis, we have yet to discuss the probable locus of the hereditary weakness. Most frequently the disease has been considered as an hereditary insufficiency of the bone-marrow. Considering, however, how widely the disease attacks the organism and that the anemia is only one symptom, this view hardly seems warranted. Others, however, have located the defect in the intestine, looking upon the disease as an hereditary deficiency or functional failure of the intestinal wall.

Without further knowledge, however, as to the pathogenesis, we can hardly hope to locate the hereditary peculiarity which leads to pernicious anemia.

Summary. 1. In the past the study of the etiology of disease has been mainly directed toward the external conditions and the results have been in many instances unsatisfactory.

2. It will certainly prove fruitful to devote more attention to the inner causes of disease, that is, to the genotype.

3. In pernicious anemia, as in many other hereditary diseases, the role of the genotype ought to be investigated. It is necessary to investigate behavior and frequency of hereditary incidence in the various diseases.

4. The two principal methods of study to this end, namely, the analysis of casuistics and method of statistical summation, are described and discussed in their application to pernicious anemia.

5. In these studies we have an important field for clinical investigation, since all our knowledge of heredity in human pathology is still in an initial stage of uncertainty with many assumptions. This important problem cannot be solved by any one investigator, but must be attacked by a systematic collaboration between clinical research and the students of racial biology.

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CHRONIC FAMILIAL HEMOLYTIC JAUNDICE OR BANTI'S DISEASE.*

BY CHARLES HARTWELL COCKE, M.D.,

ASHEVILLE, N. C.

THE following case is reported not by reason of its rarity but because of its interesting nature and the difficulty of diagnosis.

Case Report.—**FAMILY HISTORY.** The patient's maternal grandmother died at the age of sixty years from an undiagnosed condition in which there was a large spleen of some years standing. The history of jaundice in her is unreliable though probable. Patient's mother died at the age of about forty years of epidemic influenza in the fall of 1918, although it was known to at least two Asheville physicians that she had a tremendously enlarged spleen, and was

* Read before the American Climatological and Clinical Association, Atlantic City, May 1, 1924.

jaundiced for some years. An interesting and unusual observation also in this lady was the presence of palpable gall stones, demonstrated also by roentgen-ray. In this connection I might say that cholelithiasis is quite a frequent complication of familial hemolytic jaundice but not of Banti's disease. Father living and well. One brother, aged twenty years, was operated upon by Dr. J. M. Lynch (who kindly gave me the above information about my patient's mother) May 22, 1918, a splenectomy being done for a greatly enlarged spleen. The records show a clinical diagnosis in his case of Banti's disease, but laboratory and pathological studies are unfortunately lacking in this case. This young man was in my office February 9, 1924, apparently in robust health with no signs of jaundice or anemia. He promised to report to the laboratory for complete blood examination but so far I have been unable to get in touch with him again. When seen by me he was a machine operator in a local furniture factory.

PERSONAL HISTORY. The patient is young, married, white woman, aged seventeen and a half years, born and raised in Buncombe County near Asheville. Childhood infections include measles, chicken-pox and whooping-cough. The past illnesses are practically *nil* and there is no history of malaria, syphilis or typhoid fever, though the patient claims that the yellow tint of the skin has persisted for several years. The menses were established at the age of fifteen. She has been married four months.

Present illness began three days ago, February 2, 1924, when the patient complained of contracting what was thought to be an ordinary cold with some cough, but because of a disproportionate amount of prostration consulted Dr. A. T. Hipps, who discovered the enlarged spleen and jaundice, and referred the patient to my service at the Asheville Mission Hospital. The patient entered the hospital February 5, 1924, but remained only a few days and left against advice and before completion of study. She belongs to the type of person raised in the country whose fear of hospital procedure and antipathy to routine observation and study (without immediate concurrent relief symptomatically) lead to an abrupt departure from the institution before any material benefit can be derived from study of the case. This propensity for peregrination also animates their choice of numerous places of abode and an ever changing list of medical attendants, and adds materially to the difficulties of subsequently locating them for additional observation.

PHYSICAL EXAMINATION. The patient is a very poorly developed, small, badly nourished young woman, about 5 feet, tall and weighing 92 pounds. She appears more nearly to be fifteen or sixteen years of age than the first age given in the history of eighteen years, later amended to seventeen years. She is apparently in no pain and not dyspneic, though seems quite weak. The positive findings in the examination are as follows:

Eyes. Scleræ, distinctly yellow; conjunctivæ, pale yellow.

Throat. Nothing abnormal seen save slight paleness of the mucous membrane.

Skin. Is of uniformly deep lemon hue.

Heart and Lungs. Normal.

Pulse. Regular, soft, rate 80. Blood-pressure 100-72.

Abdomen. No distention of abdominal veins. Liver dulness begins at the fifth space and extends to the free border of the ribs, the edge not being felt, and no tenderness observed either in this area or elsewhere. No distention, rigidity, masses or shifting dulness in the flanks. The spleen is found uniformly enlarged by percussion and is readily felt $2\frac{1}{2}$ fingers breadth below the costal margin. It is firm, superficial, smooth, and not at all tender.

Vaginal Examination. Patient thought to be about three months pregnant.

LABORATORY REPORTS. *Urine.* Clear, deep yellow, no sediment; acid; 1020; no albumin nor sugar. Bile, small amount. (This was the usual oxidative test and probably means urobilin.)

Blood. Hemoglobin 59 per cent; erythrocytes, 2,900,000; color index, 1.01; leukocytes, 8200. Differential count (200 cell); lymphocytes, 27 per cent; large mononuclears, 5 per cent; polynuclear neutrophils, 61 per cent; eosinophiles, 7 per cent; anisocytosis, marked amount; poikilocytosis and polychromatophilia absent; but granular degeneration quite marked. No microblasts, normoblasts or macroblasts seen.

Serum Reaction. Blood Wassermann negative. Blood serum: Deeply stained yellow with bile pigment. Coagulation time: Five minutes.

Feces. Not examined but reported well colored. The provisional diagnosis of Banti's disease was made.

SUBSEQUENT COURSE. The patient remained in hospital only a few days, she was seen at my suggestion by Dr. Joseph L. Adams, attending surgeon to the hospital, but immediately upon suggestion of an operation left the hospital before completion of laboratory studies of the blood and feces.

Three days after leaving the hospital she began to cramp and bleed, and with her propensity for change, this time summoned Dr. H. G. Brookshire (to whom I am indebted for this part of my story), who diagnosed the condition as one of incomplete abortion. At his advice she was removed to the French Broad Hospital where a curettage was done by Dr. A. T. Pritchard, who told me few evidences of pregnancy existed at the time of the operation. Patient made a normal convalescence from this procedure and shortly left the hospital.

Having learned this part of the story several weeks after I last saw her, I began my efforts to find her and, after much search, she was finally located by me on March 26, the cause of my difficulty

being that she had been on the move again. Then she appeared greatly improved in both appearance and weight. Jaundice was very much lighter, pallor was definitely less and patient claimed her present weight was 100 pounds, a gain of 8 pounds. At this time she was nursing a sick husband with quite a florid measles (apparently) and promised to report to my office for further study. As she had not done this by April 11, fearing that I might again lose sight of her, I looked her up on this date, taking the same laboratory technician with me who made the original tests (Mr. O. E. Stockinger, to whom I am greatly indebted for the interest and care he showed in this and in all the laboratory work). Unfortunately I found her in bed with an acute respiratory infection (she had summoned still another physician so I was not at liberty to make a physical examination). A specimen of urine furnished this day, though deeply colored, failed to show any bile pigment. She said she felt well enough for us to take her blood. This study showed: Hemoglobin, 78 per cent; erythrocytes, 3,100,000; leukocytes, 11,300 (acute respiratory infection?); serum, stained yellow.

Fragility of Red Cells. Hemolysis was initiated at 0.50 per cent. and completed at 0.40 per cent, while a control of my own blood showed hemolysis began at 0.44 per cent and was completed at 0.36 per cent. The technic used in this test was practically Giffin and Sanford's modification of Ribierre's, great care having been taken to obtain accurate dilutions by using a serological pipette for measurements and not relying on the more inaccurate method of drops, the necessity of extreme accuracy being judged essential. No estimation of the blood cholesterol¹ was made.

Discussion. As stated previously, the first impression gained from clinical study of the case was that we were dealing with a case of Banti's disease of familial origin. Realizing, however, the inadequacy of the grounds upon which to base a final diagnosis, it became necessary to look the patient up for further blood study, with results as just stated. All observers since Chauffard have agreed upon the necessity for determining hemolysis to hypotonic salt solutions as essential for the diagnosis of hemolytic jaundice. And yet while in retrospect this case seems to present all the necessary elements for the diagnosis of hemolytic jaundice; to wit, family incidence, adolescent appearance, splenomegaly, moderate to considerable jaundice, symptomless course, some anemia with unchanged white count and differential picture, bile pigment in the urine at one time (absent at last observation) with lowered resistance of the red blood cells to hypotonic salt solutions, it is well to mention as pointed out by Held² that the following variations from such a typical picture may obtain:

(a) Acholuric jaundice and splenomegaly present with polycythemia instead of anemia.

(b) Evidence of increased blood destruction but no change in the resistance of the red blood cells.

(c) Evidence of increased blood destruction but no jaundice. And further it should be noted that in some cases of hemolytic jaundice the blood-picture may so very strongly resemble pernicious anemia as to puzzle good clinicians.

In reporting this case, it is not my purpose to settle a nosological uncertainty or define a clinical complex. As subsequent studies made under somewhat difficult conditions as well as a cursory review of the literature available to me on the subject of Banti's disease and chronic hemolytic jaundice have convinced me of the error in my earlier conclusion, based almost entirely on clinical grounds and routine laboratory tests, it has seemed to me not altogether inappropriate to raise the question of the difficulty of distinguishing the various splenomegalies associated with jaundice and little else symptomatically. As my study of this case continued, I found that apparently the difficulty in diagnosing Banti's disease is in direct ratio to one's acquaintance with the rather voluminous literature on this subject and the other sometimes easily confused conditions. Nor need one hesitate to confess error in his original conclusions as to Banti's disease, as Osler withdrew one of his cases from an earlier report on splenic anemia and revised the diagnosis to pernicious anemia.

While neither Banti's disease nor familial hemolytic jaundice are such rarities that they call for individual case reports when seen, the difficulties presented to me in this case are such as may well confront anyone not equipped for rather complete laboratory studies. Any effort properly to differentiate Banti's disease and hemolytic jaundice seems hopeless without such aid, at least in the early stages of Banti's disease. To begin with there is no symptomatology ordinarily attached to idiopathic splenomegaly. By the time the second stage of Banti's disease is reached, generally known as splenic anemia, the similarity of the course of the symptoms in Banti's disease and hemolytic jaundice is sufficient to cause confusion. Banti's disease usually begins in early adult life, hemolytic jaundice somewhat earlier, but may not make its appearance until early adult life. There is the enlarged spleen in both, jaundice may be present, usually milder in the hemolytic jaundice, but this is subject to periodic variations in both conditions, and in the case of Banti's disease does not seem to be dependent upon the liver involvement which is a third stage development. In both cases the patient may be more icteric than sick. In the case here reported, the degree of jaundice was quite marked when the patient was first seen and was far removed from that "mere cosmetic blemish" which Türk mentioned as quite common in hemolytic jaundice. And this too despite the absence of acholuric crises.

There may be an absence of the usual hematemeses in Banti's

and also of the acholuric crises in hemolytic jaundice, the two symptoms which relatively speaking should give the clinical clue to the proper diagnosis though rarely, by way of adding to the confusion, there may be hemorrhages in hemolytic jaundice. My patient has had neither. There is a mild anemia in both, although more severe anemias are more likely to be found in the acquired rather than the familial type of hemolytic jaundice, approaching the pernicious anemia picture. The hemoglobin in Banti's disease is quite low with consequent low color index; it more nearly corresponds with the degree of red cell loss in hemolytic jaundice. In Banti's disease, at first there is no change in the number of white cells though later there is well-defined leukopenia; in hemolytic jaundice the leukocytes are normal in number, increased or decreased³ though Held⁴ states that there is a neutrophilic leukocytosis. Neither was this nor any leukopenia present in my case. The slight eosinophilia found here must go unexplained for lack of opportunity for study. Urobilin is supposedly a constant finding in hemolytic jaundice, albuminuria a frequent one in Banti's disease. Two examinations of the urine (February 6 and April 11) failed to show any albumin. The February examination of the urine showed a *small* amount of urobilin, the April examination, none. What influence, if any, did the pregnancy have upon the picture? The relief of this additional strain resulting from abortion was certainly followed by a very material improvement.

The distinctive laboratory finding is the presence in hemolytic jaundice of an increased number of reticulated red cells (vital staining) which are normal in Banti's disease and an increased fragility of the red cells to hypotonic salt solutions (while in Banti's the resistance seems to be normal, or perhaps increased) and a diminished blood cholesterol according to Neilson and Wheelon.⁵

In passing, it is worthy of note that this fragility of the red cells, which is such a marked characteristic in *familial* hemolytic jaundice, may be quite absent in the *acquired* type of the disease, with which we are not here concerned.

Though Ribierre⁶ first clearly summarized the existing knowledge concerning hemolysis, it is curious enough that despite his exhaustive study of blood resistance in jaundice, he overlooked the most important diagnostic discovery in connection with his subject; in other words, he failed to show the very constant increased fragility present in hemolytic jaundice. Chauffard⁷ in 1907 made this interesting discovery, which has been confirmed by practically all subsequent observers. The technic, using the hypotonic salt solutions is relatively simple; the greatest precaution, however, should be taken in order to assure accuracy in the solutions and since slight variations are important, a known control should be run with each case. The literature confirms the value of the test as a method of distinguishing hemolytic jaundice from its simulators. Giffin

and Sanford⁸ found the averages of initial and complete hemolysis in controls to be 0.44 per cent salt solution and 0.365 per cent while in 23 cases of known hemolytic jaundice the figures were 0.478 initial, 0.413 complete. It is interesting, however, that while three of the 23 cases of hemolytic jaundice cases failed to show increased fragility, no case showed increased resistance. The average figures in 14 cases of splenic anemia very carefully selected were 0.402 per cent, 0.316 per cent. In none was initial hemolysis begun above 0.44 per cent and complete at 0.36 per cent, a definite increase in resistance.

Another interesting feature of Giffin and Sanford's report is that relatives of 4 patients with hemolytic jaundice showed an increased fragility. Two of these 4 relatives had no symptoms whatever of the disease and in 2 of them the symptoms were not noted until they were eighteen and twenty years of age respectively, an indication of a definite hereditary factor even in cases occurring in later life.

What of the familial incidence of Banti's disease? Most authors state that heredity plays no part in the disease though Lyons⁹ states that a family incidence has been noted by Brill, Bovaird, Collier, Wilson, and others (but I have not found the original references), although this seems to be unusual. Hemolytic jaundice may be congenital but not hereditary¹⁰ and as stated may be hereditary but not appearing for some time after birth.

While a great many clinicians are willing to accept Osler's assumption that primary or idiopathic splenomegaly and anemia (the so-called splenic anemia) and splenomegaly anemia and cirrhosis of the liver with ascites are three stages of the same condition to which Banti first called attention about forty years ago, and to which some years later his name was attached, there are not lacking numbers of clinicians and pathologists who dissent from the belief that there is such an entity as Banti's disease. Naunyn would refuse it clinical identity, while Norris, Symmers and Shapiro¹¹ in addition to denying that there is such an entity as Banti's disease, claim that it really represents a splenic manifestation of syphilis with or without liver sclerosis, and that all the clinical and anatomical requirements of the disease as originally presented by Banti are adequately satisfied by syphilis. Against their evidence and opinion are number of cases reported, not only with negative Wassermanns, but presenting no evidence of syphilis whatever. Eli Moschowitz¹² would do away with the present terminology, Banti's disease, and substitute therefore, Banti's Complex. As many authors are prone to the assumption that the absence of known etiology is a distinguishing criterion of Banti's disease, he says there is no reason for differentiating Banti's disease from other splenomegalies associated with anemia on such a ground, to wit, no definite etiology. A nosological distinction based on whether a disease has a known or

unknown etiology has no *raison d'être* in clinical medicine. He would regard Banti's disease as a nosological and clinical entity, due to both known and unknown causes.

Banti's disease unfortunately presents no typical course, no diagnostic symptoms and, while its pathology is not specific, does differ essentially from other splenomegalies of known origin, such as malaria or syphilis.

Naegeli¹³ states that he agrees with numerous observers who claim that they have never seen a case that had to be diagnosed Banti's disease, and he is further "more and more convinced that etiologically widely different chronic inflammatory processes of the portal vein produce the picture and secondarily produce a sclerosis of the spleen in itself not characteristic." In dissenting from Banti's claim of characteristic pathology, Naegeli says that among German authors only Senator, Grawitz and Umber agree with Banti's ideas.

Sir Berkeley Moynihan in his Bradshaw lecture¹⁴ assents to Osler's definition of the disease as an intoxication of unknown nature, characterized by great chronicity, primary progressive splenomegaly which cannot be correlated with any known cause, anemia of secondary type with leukopenia, marked tendency to hemorrhage and in many cases a terminal stage with cirrhosis of the liver and jaundice and ascites. As to the pathogenesis the most striking fact known about Banti's disease is that removal of the spleen so frequently results in a cure. The same is perfectly true of hemolytic jaundice. This may be accounted for either on the assumption that the disease is either primarily or essentially located in the spleen or that the spleen modifies the action of some agency situated elsewhere in the body. So far no conclusive evidence has been brought forward incriminating a specific microbe, though Hollins argues in favor of the colon bacillus as the cause. Gibson¹⁵ found a streptothrix in six cases, but failed to reproduce the condition experimentally in animals with this streptothrix, nor has anyone confirmed Hollins' work.

Yates, Banting and Kristjanson¹⁶ report isolation in four instances of a diphtheroid organism resembling that repeatedly isolated by them from lymph nodes in Hodgkin's disease. I can find no confirmation of this finding. However, these authors make no claim to the establishment of etiological relationship.

W. J. Mayo¹⁷ states that despite the fragmentary and inconclusive nature of his information, from quite an extensive mass of material passing through his hands, he has the impression that generalized splenic fibrosis and thrombophlebitis are the result of many causes and the pathological changes in the spleen, the liver, and the blood are regularly developed regardless of the primary etiological factors.

It is very interesting to speculate upon the unknown etiology of these conditions and the possible relevancy of the fact that the only known cure, despite the frequent benign course, for both of them is

splenectomy—a fact that may some day help solve the enigma of the spleen's true function.

Summary. A case report is given of a young woman presenting the jaundice-splenomegaly complex. There is a family incidence of a similar condition in one brother, mother, and grandmother. An uninforming blood picture, and unknown etiology, and a symptomless course points either to Banti's disease or familial hemolytic jaundice. The difficulties of differentiation by clinical methods only are pointed out. The increased hemolysis of the red blood cells to hypotonic salts solution points to the conclusion that hemolytic jaundice is the correct diagnosis; as in Banti's disease, if there is any change in blood resistance, it is in the nature of an increase. The importance of this test is emphasized. The difficulties of a clinical diagnosis of Banti's disease until the terminal stages are reached is discussed.

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THE EFFECT OF SPLENECTOMY IN EXPERIMENTAL ANEMIA.

BY MEYER BODANSKY, PH.D., HENRY C. HARTMAN, M.D.,

AND

JOHN D. GLECKLER, M.D.,
GALVESTON, TEXAS.

(From the Laboratory of Biological Chemistry and the Department of Pathology,
University of Texas.)

MUCH evidence has been accumulated to show that the resistance of erythrocytes is increased after splenectomy. Pearce, Austin and Krumbhaar¹ found that the effect of a powerful hemolytic serum upon the recently splenectomized animal is not widely different from

that upon the normal animal. In both, the blood is laked freely and death results in a few hours. However, one month and more after splenectomy the red cells manifest an increased resistance to hemolysis. Banti,² Vast,³ and Joannovics⁴ have observed that the splenectomized animal is more resistant than the normal animal to the hemolytic action of toluylendiamine. Similar observations have been recorded by Pugliese and Luzzatti⁵ in the case of pyrocin (acetylphenylhydrazine). Kolmer⁶ has determined that the resistance of erythrocytes of dogs to the hemolytic activity of cobra venom is increased after splenectomy, the increased resistance usually persisting for about three weeks, when apparently coincident with the anemia following splenectomy, the resistance gradually decreases to normal or slightly beyond.

In the present investigation, we have compared the onset and progress of experimental anemia in normal and splenectomized animals with particular reference to the rate of red cell destruction and to the degree of erythropoiesis as judged by the presence of normoblasts in the circulation and by changes occurring in the bone marrow.

Two types of experimental anemia were studied in this connection. It has been shown previously^{7,8} that in acetylphenylhydrazine poisoning there is rapid red cell destruction with relatively slight or no liver injury, whereas in symmetrical di-isopropylhydrazine-hydrochlorid intoxications, there is initially anhydremia and severe liver injury, followed by a more or less marked anemia. In each series of experiments 3 dogs were splenectomized and after a shorter or longer period of recovery, anemia was induced by the injection of either acetylphenylhydrazine or symmetrical di-isopropylhydrazine-hydrochlorid. Two dogs served as controls in each series. Both following splenectomy and during the course of anemia, determinations were made of the erythrocyte and leukocyte counts, hemoglobin (Newcomer method) and differential count, including nucleated red cells when present. For the purpose of economizing space the differential leukocyte counts have not been included in the following tables. The animals were maintained in proper nutritive condition on an adequate diet of "table scraps," fresh meat and yeast.

Musser⁹ and Musser and Krumbhaar¹⁰ have shown that following splenectomy a secondary anemia usually develops almost immediately and reaches its greatest severity in from three to six weeks. The observations in the case of most of our dogs are in accord with this view. In one animal (Dog 1), a very pronounced anemia was observed one week after splenectomy. Regeneration occurred gradually and was not complete at the end of two months. As in the work of Musser and Krumbhaar, a temporary leukocytosis was observed following splenectomy. There were frequently irregular

increases in the lymphocyte and eosinophile counts; but these were not constant features. It is pointed out by Pearce, Krumbhaar and Frazier¹¹ that the stage of repair of the anemia following spleen extirpation is not characterized by the constant appearance in the peripheral blood of nucleated or other abnormal types of red cells. While this is in agreement with many of our observations, it is to be noted that in the case of one animal (Dog 7), nucleated cells appeared in all examinations following splenectomy, as many as 8 normoblasts being found in counting 100 leukocytes.

Individual animals may show considerable variations in the rate of recovery from experimental anemia and in the number of immature cells appearing in the circulation during the periods of onset and recovery. However, these variations do not seem to differ appreciably in normal and in splenectomized animals. Insofar as the rate of blood destruction is concerned, our observations are more nearly in accord with those of Krumbhaar, Musser and Pearce¹² on hemolytic immune serum anemia than with the work of Banti, Vast, and Joannovics. It is to be noted that no striking differences in the destructive action of symmetrical di-isopropylhydrazine and acetylphenylhydrazine were observed in recently splenectomized animals than in those after relatively long periods of recovery from splenectomy.

The changes in the bone marrow are presented briefly in the following protocols. We have also included the histological findings of the liver, kidney and spleen. In a previous communication,⁷ it was shown that acute intoxications with acetylphenylhydrazine produce marked anemia without liver injury. It appears, however, that in chronic intoxications with a high degree of anemia, hepatic and renal involvement may occur.

Summary. Removal of the spleen does not appear to modify appreciably the rapidity of red cell destruction due to acetylphenylhydrazine or to symmetrical di-isopropylhydrazine-hydrochlorid. Individual animals, whether splenectomized or unsplenectomized, exhibit considerable variations in the rate of recovery from anemia and in the degree of erythropoiesis during the progress of the anemia.

Dog 1. Four months after splenectomy (killed). Acetylphenylhydrazine anemia. Liver: Very slight granular and fatty degeneration and small amount of hematogenous pigment, otherwise normal. Moderate cellular hyperplasia and hematogenous pigmentation of bone marrow.

Dog 9. Three months after splenectomy (died). Acetylphenylhydrazine anemia. Liver: Fatty changes and very marked hematogenous pigmentation. Bone marrow: Very little hematogenous pigment, marked hyperplastic changes and nucleated erythrocytes. Kidney: Degeneration of renal epithelium, early nephrosis.

TABLE I.—DOG 1, MALE, WEIGHT 7.8 KILOS.

Date, 1923-24.	Erythrocytes in millions.	Hemoglobin in grams.	Leukocytes.	Nucleated erythrocytes.*	Remarks.
Oct. 31	6.43	10.80	33,000	0	Splenectomy.
Nov. 7	3.63	7.22	43,000	0	
Nov. 10	3.70	7.22	38,200	0	
Nov. 15	3.86	7.11	37,800	2	
Nov. 21	3.90	6.72	18,850	0	
Nov. 27	4.03	7.11	19,150	0	
Dec. 18	4.58	9.50	19,800	0	
Jan. 8	5.20	10.50	20,700	1	Injected 300 mg. acetylphenylhydrazine.
Jan. 9	4.84	9.50	17,400	0	
Jan. 11	3.82	5.45	27,100	1	
Jan. 14	2.11	3.92	22,800	7	
Jan. 16	1.90	3.66			
Jan. 17	1.90	3.42	18,000	14	
Jan. 21	2.16	4.25	8,800	0	
Jan. 26	3.52	6.80	11,520	0	
Feb. 4	3.52	8.00	17,920	0	
Feb. 20	4.40	8.80	12,800	0	Injected 200 mg. acetylphenylhydrazine.
Feb. 25	2.96	5.72	25,600	0	
Feb. 26	2.56	3.92†	3	
Mar. 4	2.08	4.00	25,600	0	Killed by heart puncture.

DOG 9, MALE, WEIGHT 7.1 KILOS.

Dec. 18	8.30	15.05	18,400	0	Splenectomy Dec. 21
Jan. 8	7.23	14.80	27,600	0	
Jan. 28	6.40	14.20	18,400	1	
Feb. 6	6.20	14.65	22,400	2	
Feb. 10	Injected 250 mg. acetylphenylhydrazine.
Feb. 13	4.80	9.95	15,000	11	
Feb. 16	2.64	6.04	16	
Feb. 19	2.88	5.75	29	
Feb. 20	Injected 200 mg. acetylphenylhydrazine.
Feb. 21	2.64	5.68	28	
Feb. 25	2.32	5.20	14	Injected 200 mg. acetylphenylhydrazine.
Feb. 26	1.76	3.21	16	
Mar. 4	2.32	4.40	22,400	49	
Mar. 7	2.32	4.37	22,400	16	Injected 400 mg. acetylphenylhydrazine.
Mar. 10	1.96	3.40	18	
Mar. 11	1.48	2.80	8	
Mar. 14	1.24	2.72	11	Dog died March 16.

DOG 13, FEMALE, WEIGHT 11.5 KILOS.

Mar. 24	4.80	9.50	32,000	0	Splenectomy March 25.
Apr. 3	5.20	9.80	21,600	0	Injected 300 mg. acetylphenylhydrazine.
Apr. 4	4.96	8.90	22,400	0	
Apr. 7	3.28	5.80	0	
Apr. 9	2.08	4.60	3	
Apr. 11	2.72	5.80	40,000	5	
Apr. 14	2.96	6.20	24,000	0	
Apr. 18	3.68	8.00	25,600	0	Injected 300 mg. acetylphenylhydrazine.
Apr. 19	4.16	8.00	14,000	0	
Apr. 21	3.44	7.50	16,000	0	Injected 400 mg. acetylphenylhydrazine.
Apr. 23	2.96	4.75	8	Injected 400 mg. acetylphenylhydrazine.
Apr. 24	1.70	3.20	7	
Apr. 26	0.82	1.50	2	Dog died April 27.

DOG 12, MALE, WEIGHT 5.3 KILOS.

Feb. 6	6.72	14.60	20,000	0	
Feb. 10	6.72	14.60	23,200	0	Injected 200 mg. acetylphenylhydrazine.
Feb. 13	4.32	9.10	24,000	2	
Feb. 16	2.40	6.33	24,400	1	
Feb. 19	2.80	7.10	12,800	8	Injected 200 mg. acetylphenylhydrazine.
Feb. 21	3.28	7.32	14,000	3	
Feb. 25	2.80	6.30	2	Injected 200 mg. acetylphenylhydrazine.
Feb. 26	2.32	6.00	8	
Mar. 1	1.95	3.16	31,200	1	

DOG 16, FEMALE, WEIGHT 11.5 KILOS.

Apr. 22	5.92	10.20	16,000	0	Injected 300 mg. acetylphenylhydrazine.
Apr. 23	4.94	9.00	16,400	0	
Apr. 26	3.68	8.50	19,200	1	
Apr. 28	3.20	8.00	19,000	11	
May 3	3.66	8.12	32,000	1	Injected 300 mg. acetylphenylhydrazine.
May 8	3.20	7.60	1	Injected 400 mg. acetylphenylhydrazine.
May 10	2.10	4.40	0	
May 13	2.08	4.23	40	
May 15	2.40	4.45	18,000	2	
May 18	2.16	4.20	16,000	0	

* Number found in counting 100 leukocytes plus nucleated erythrocytes.

† In a number of instances accurate leukocyte counts could not be made owing to the presence of large amounts of cell debris.

Dog 13. One month after splenectomy (died). Acetylphenylhydrazine anemia. Marked fatty and degenerative changes in the liver with complete replacement of hepatic tissue in small areas, also hematogenous pigmentation. Bone marrow: Marked hyperplasia and hematogenous pigment, small number of nucleated red corpuscles.

Dog 12. Unsplenectomized. Acetylphenylhydrazine anemia. Liver: Large amount of hematogenous pigment and very slight fatty change. Spleen: Large amount of hematogenous pigment and slight cellular hyperplasia. Cellular hyperplasia of bone marrow, nucleated erythrocytes.

TABLE II.—DOG 7, MALE, WEIGHT 7.2 KILOS.

Date, 1923-24.	Erythrocytes in millions.	Hemoglobin in grams.	Leukocytes.	Nucleated erythrocytes.*	Remarks.
Dec. 7	5.73	10.96	31,300	0	Splenectomy.
Dec. 14	5.89	11.05	27,800	0	
Dec. 19	5.79	11.15	14,700	5	
Jan. 11	5.12	9.47	30,000	1	
Feb. 1	4.30	8.60	21,000	5	
Feb. 5	4.32	8.45	21,200	6	
Feb. 13	4.16	8.75	23,000	8	
Injected 200 mg. symmetrical di-isopropylhydrazine-hydrochlorid.					
Feb. 14	5.28	9.30	16,000	0	
Feb. 17	4.39	7.46	20,300	1	
Feb. 20	3.60	7.06	24,000	4	Injected 200 mg. sym. compound.
Feb. 22	3.36	7.46	32,000	2	
Feb. 27	3.20	7.12	33,600	3	
Mar. 5	2.88	6.65	22,400	14	
Mar. 12	3.68	7.87	17,600	5	Injected 300 mg. sym. compound.
Mar. 14	4.32	8.45	16,800	2	
Mar. 18	3.68	8.40	16,000	0	
Mar. 25	2.32	4.61	22,400	1	Injected 300 mg. sym. compound.
Mar. 31	2.72	5.60	24,000	1	
Apr. 7	2.98	5.70	6,400	1	Killed.

DOG 6, MALE, WEIGHT 6.0 KILOS.

Dec. 7	8.32	15.05	15,100	0	Splenectomy.
Dec. 14	8.59	15.55	16,400	0	
Dec. 19	8.54	14.75	40,000	0	
Jan. 11	6.83	12.00	31,200	0	
Jan. 30	6.24	10.50	16,000	2	
Feb. 5	5.80	10.16	27,200	3	
Feb. 13	5.92	9.95	16,000	1	
Injected 150 mg. symmetrical di-isopropylhydrazine-hydrochlorid.					
Feb. 14	6.10	10.10	20,000	1	
Feb. 17	5.82	11.80	22,800	0	
Feb. 20	4.48	9.25	23,200	2	Injected 200 mg. sym. compound.
Feb. 22	4.16	8.43	16,000	0	
Feb. 29	5.44	9.65	15,000	0	
Mar. 12	5.12	8.75	12,800	0	Injected 300 mg. sym. compound.
Mar. 14	5.12	8.75	25,600	0	
Mar. 18	4.32	8.45	12,000	1	Injected 300 mg. sym. compound.
Mar. 24	3.60	7.10	25,600	14	
Mar. 25	3.60	6.85	32,000	14	Dog died March 27.

DOG 15, FEMALE, WEIGHT 13.0 KILOS.

Apr. 14	6.44	13.58	14,000	0	Splenectomy on Apr. 16.
Apr. 18	6.40	13.65	28,000	0	
Injected 180 mg. symmetrical di-isopropylhydrazine-hydrochlorid.					
Apr. 19	5.92	11.90	44,000	0	
Apr. 21	5.12	11.20	28,000	0	
Apr. 23	4.80	10.66	17,200	1	Injected 200 mg. sym. compound.
Apr. 24	5.36	11.20	25,600	1	
Apr. 26	4.80	8.60	25,600	4	
Apr. 29	3.44	7.98	36,000	6	
May 2	3.04	7.00	28,000	23	Injected 300 mg. sym. compound.
May 5	3.36	6.70	25,600	2	
May 9	3.36	6.70	22,400	5	Injected 300 mg. sym. compound.
May 21	4.00	7.42	18,200	2	

TABLE II.—DOG 7, MALE, WEIGHT 7.2 KILOS—(Continued).

DOG 2, FEMALE, WEIGHT 7.8 KILOS.					
Date, 1923-24.	Erythrocytes in millions.	Hemoglobin in grams.	Leukocytes.	Nucleated erythrocytes.*	Remarks.
Nov. 10	7.89	14.60	13,500	0	
Nov. 12	Injected 200 mg.	symmetrical	di-isopropylhydrazine-hydrochlorid.		
Nov. 13	9.55	12.70	33,350	5	
Nov. 14	9.20	12.70	22,400	5	
Nov. 15	8.57	11.45	23,400	3	
Nov. 16	6.88	10.90	17,850	2	
Nov. 17	6.30	11.00	25,700	16	
Nov. 19	Injected 150 mg.	symmetrical	di-isopropylhydrazine-hydrochlorid.		
Nov. 20	6.69	10.55	18,900	20	
Nov. 22	6.68	9.35	14,600	18	
Nov. 24	6.65	9.30	17,000	24	
Nov. 26	5.42	8.30	21,000	12	
Nov. 30	5.00	8.00	12,700	31	
Dec. 3	3.46	7.13	16,200	14	
Dec. 6	4.37	8.30	20,800	14	
Dec. 10	4.43	9.68	15,800	11	Injected 135 mg. sym. compound.
Dec. 13	5.71	10.73	14,000	6	
Dec. 14	3.18	7.43	15,500	1	
Dec. 17	4.00	7.40	21,300	10	
Jan. 4	5.92	12.70	13,500	0	
Feb. 4	7.20	13.80	14,000	2	Injected 180 mg. sym. compound.
Feb. 10	6.40	12.70	12,800	2	
Feb. 13	5.12	9.75	12,800	3	
Feb. 16	5.60	11.05	21,000	39	
Feb. 20	4.56	10.35	16,000	38	
Feb. 27	4.16	10.55	19,600	2	
Mar. 5	4.00	10.30	16,000	8	
Mar. 11	5.44	12.70	16,000	3	Injected 350 mg. sym. compound.
Mar. 18	4.64	10.10	13,760	10	
Mar. 24	3.84	8.00	19,200	24	
Mar. 31	3.20	7.91	19,200	12	
Apr. 7	4.00	8.65	19,200	1	Dog autopsied.

DOG 14, MALE, WEIGHT 11.5 KILOS.

Apr. 18	6.40	12.00	8,000	0	
Apr. 19	Injected 170 mg.	symmetrical	di-isopropylhydrazine-hydrochlorid.		
Apr. 21	5.76	11.00	12,000	0	
Apr. 21	4.30	8.56	16,000	0	
Apr. 23	4.40	8.50	19,200	12	Injected 200 mg. sym. compound.
Apr. 24	5.28	9.65	20,000	11	
Apr. 26	4.32	8.42	16,000	8	
Apr. 29	4.00	7.46	11,200	6	
May 2	4.30	8.00	9,600	1	Injected 250 mg. sym. compound.
May 5	4.80	9.12	16,000	4	
May 9	4.00	7.86	12,800	2	
May 21	4.00	7.54	12,800	0	

Dog 7. Three and three-quarters months after splenectomy (killed). Symmetrical di-isopropylhydrazine anemia. Liver: Marked fatty change and slight fibrous change. Bone marrow: Hematogenous pigmentation, cellular hyperplasia and nucleated red cells. Slight fatty change in the kidney.

Dog 2. Unsplenectomized. Symmetrical di-isopropylhydrazine anemia. Liver: Numerous areas of complete necrosis of hepatic cells, moderate fatty degeneration, some hematogenous pigment and early sclerotic changes. Bone marrow: Hyperplasia and hematogenous pigment, a great many nucleated red cells in bone marrow. Kidney: Slight fatty degeneration in the tubular epithelium and early sclerotic changes. Cellular hyperplasia in the spleen,

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THE SEDIMENTATION RATE OF ERYTHROCYTES.

BY I. T. ZECKWER, M.D.,

AND

HELEN GOODELL, B.S.,

BOSTON.

(From the Laboratory of Pathology, Long Island Hospital, Boston.)

THE rate at which red cells gravitate, when citrated blood is allowed to stand, has been widely used in Germany and Scandinavian countries as a clinical laboratory procedure of diagnostic value under the designation of B.S. test (Blutkörperchensenkungsgeschwindigkeit), or determination of the sedimentation rate of red cells. In general, it has been claimed to be of value in the diagnosis of malignant tumors, tuberculosis, acute inflammations and pregnancy. Gynecologists have particularly emphasized the usefulness of determining this suspension stability of the blood in differentiating acute from chronic infections of the pelvic organs as a guide for surgical interference, and in differentiating inflammatory from non-inflammatory conditions. In tuberculosis it has been used as an indication of the extent of the process. It has likewise been claimed to be of diagnostic value in such a wide range of pathological conditions that it would seem that foreign investigators have become overenthusiastic and that there is need for examining more critically just what are the limits of usefulness of the test. It was, therefore, with the aim of evaluating this procedure that a number of determinations were made on patients presenting a variety of conditions.

The method as used by the Germans necessitates the use of calibrated tubes of special dimensions, which are extremely difficult to

secure in America, and consequently but few determinations have been made in this country. Falraeus,¹ who originated the method, employs a glass tube 17 cm. in length with internal diameter of 9 mm. and graduated at 0.1-cm. intervals. Two cubic centimeters of 2 per cent sodium citrate solution are placed in the tube and blood from a vein is introduced up to the 10-cc mark. The tube is inverted to mix the blood with the citrate and allowed to stand. The height of the clear plasma layer above the column of red cells is read at definite intervals of time. Another method in common use abroad is used by Linzenmeier.² It consists in using special tubes necessitating the use of only 1 cc of blood. The time is noted at which the level of red cells reaches definite marks, noted as millimeter height of the plasma column. Westergren³ has originated another micro method, using special syringes, pipettes and stand.

Because the German apparatus is practically unavailable and seems unnecessarily cumbersome, we have used a simple method which requires only ordinary apparatus. We have found that the sedimentation rate can be quite accurately and satisfactorily determined with the commonly used 15 cc centrifuge tube graduated at 0.1 cc intervals. Slight inaccuracies, such as difference in diameters of tubes are negligible sources of error as it will be seen later that it is not justifiable to place any significance upon small variations from the normal.

In introducing a new method and therefore a new scale of readings for normal and pathological cases, we do not feel that we are introducing unnecessary confusion, as no other method has yet become established in America, and even abroad the readings by different methods are not comparable on account of the fact that some investigators denote the amount of sedimentation at varying intervals of time, while others express the rate as numbers of hours and minutes required for the cells to reach various marks. Even when the former method is employed, since different investigators use tubes of different diameters and read the column of plasma as centimeters in height instead of the volume in cubic centimeters, comparable results are not obtained, and consequently readings considered as a standard of normal by one method are not applicable to interpretations of rates determined by other methods. The method we have used, in which the reading is expressed as cubic centimeters of red cells in definite intervals of time requires less effort than one in which repeated examinations of the tube are necessary to determine the time at which the cells reach given points, and the unit being a standard one of volume does not necessitate the use of a tube of special caliber.

Procedure. Two cubic centimeters of 3 per cent sodium citrate solution are placed in a 15-cc centrifuge tube graduated at 0.1 cc intervals. Blood from the patient's vein is allowed to run in up to the 10 cc mark. The tube is inverted in order to mix completely

the blood and citrate, and the mixture is allowed to stand. The time is noted. Readings of the height of the red cells are made at the end of one hour. If the height of the plasma is found to be slightly above or below the 10-cc mark, the readings for the red cells are corrected accordingly. It is to be noted that readings in this method are for cubic centimeters of red cells, as in the centrifuge tubes the readings progress upward, while the special German tubes are calibrated downward and readings are made of the plasma column.

Results. The difference in sedimentation rates of different bloods is often quite spectacular, and from numerous determinations it is evident that an increased rate has definite pathological significance. The reading at the end of twenty-four hours appears to have but little value, except to indicate cell volume, this reading being directly proportional to the volume per cent of cells in the blood. The reading at the end of one hour is the most important one and the one we have taken as a standard. Probably a half hour reading in addition would be a good procedure, as within the first hour the difference between normal and pathological blood is most striking, and in cases with very rapid rates almost the maximum amount of sedimentation occurs in this short interval, while in normal blood the sedimentation has often scarcely begun.

Observations have been made in 125 individuals, and from these it has been possible to form an estimate of the value of the procedure, and to obtain a fair idea of the normal range and the readings in various pathological conditions. In Tables I, II, III and IV, cases have been grouped according to the rate of sedimentation. It will be seen that in Table I, comprising cases with the fastest rates, every case showing a rate faster than 4.5 cc was associated with pregnancy, malignant tumor, tuberculosis, or inflammatory exudate. The zone from 4.5 to 5.5 cc as charted in Table II and indicated in chart by a shaded zone, includes chiefly pathological cases but also a few doubtful cases. In this zone 21 out of 28 cases fell under the category of cancer, pregnancy or inflammation, only 7 showing no definite evidence of these conditions though they were far from normal individuals, so that there is a high degree of probability that a person having a rate under 5.5 and above 4.5 cc has one of the above conditions present. Table III and IV give the types of conditions associated with the slower rates, only occasional cases of inflammation, tumor, or pregnancy falling within these zones. Many healthy individuals have a very slow rate. This apparently has no significance, only the increased rate being of importance.

The chart represents graphically the upper and lower limits of sedimentation rates in different conditions grouped under five heads, the range being: (1) from 3 to 6 cc in tuberculosis; (2) from 3 to 6 cc in acute inflammatory processes other than tuberculosis; (3) from

2 to 7 cc in malignant tumors; (4) from 3 to 8 cc in pregnancy; (5) from 4.5 to 9.8 cc in all other conditions. Although the range in each condition is wide, the average rates of 4.2 cc in cancer, 4.3 cc in acute inflammatory processes, and 4.4 cc in tuberculosis are far below the average of 7.1 cc in the fifth group which includes largely healthy people.

TABLE 1.—CASES SHOWING SEDIMENTATION RATE OF 2 TO 4.5 CC IN FIRST HOUR.

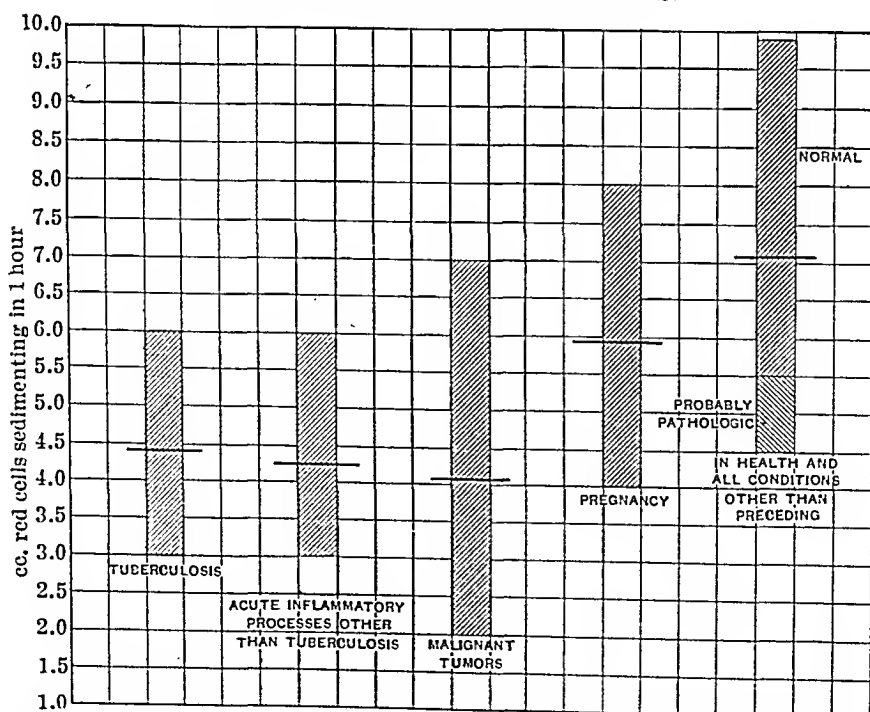
Case No.	Sex.	Age.	Chief clinical and pathological findings.	No. cc red cells sedimenting in first hour.
18	M.	45	Chronic pulmonary tuberculosis for eight years	4.34
19	M.	61	Autopsy: Pulmonary tuberculosis with cavitation; pleural effusion	4.15
21	F.	84	Autopsy: Epithelioma of face; chronic pulmonary tuberculosis	3.88
33	F.	22	Pregnant, at term	3.90
35	F.	73	Autopsy: Extensive epithelioma of ear; pulmonary tuberculosis with cavitation	4.00
37	M.	84	Autopsy: Carcinoma of ampulla of Vater, many metastases in liver	3.40
41	F.	60	Autopsy: Advanced carcinoma of uterus, formation of rectovaginal fistula	3.20
42	F.	60	Pelvic tumor, probably carcinoma	3.40
47	F.	43	Autopsy: Epidermoid carcinoma of buccal cavity; no metastases	3.40
60	F.	47	Autopsy: Carcinoma of cervix, extension to bladder and rectum	3.60
64	M.	65	Epithelioma of ear	4.00
65	M.	58	Carcinoma of pancreas; cachexia	2.10
71	F.	65	Carcinoma of breast; axillary lymph nodes involved	4.40
84	F.	7	Acute tonsillitis; gonococcal vaginitis	4.40
89	M.	80	Bronchopneumonia	4.40
93	M.	68	Autopsy: Pulmonary tuberculosis, lobar pneumonia with lung abscess; before death: white blood cells, 50,000; polymorphonuclears, 95 per cent	3.00
94	M.	6	Acute cervical lymphadenitis; white blood cells, 18,000	3.80
96	M.	63	Carbuncle of neck; extensive cellulitis	4.10
100	F.	48	Carcinoma of stomach resected; autopsy: Metastases in lymph nodes, acute miliary tuberculosis of lungs, abscess of leg with cellulitis (hemolytic streptococcus)	3.00
101	F.	70	Syphilis; aortic aneurysm	4.20
103	F.	33	Carcinoma of uterus; extension to bladder; distant metastases	4.20
108	M.	57	Advanced pulmonary tuberculosis	4.10
110	M.	27	Pyonephrosis; very septic	4.40
121	M.	37	Postoperative infection of skin graft; very septic	4.30
123	M.	53	Advanced pulmonary tuberculosis	3.40
125	M.	65	Sarcoma of jaw, sloughing	3.00

The clinical diagnoses of these patients have in many cases been corroborated by autopsy, and the postmortem findings gave proof that the increased rate parallels the severity of the process. These

TABLE II.—CASES SHOWING SEDIMENTATION RATES OF 4.5 TO 5.5 CC
IN FIRST HOUR.

Case No.	Sex.	Age.	Chief clinical and pathological findings.	No. cc red cells sedimenting in first hour.
10	F.	22	Pregnant eight months	5.42
13	F.	67	Ulcerating epidermoid carcinoma of umbilical region	5.49
14	F.	56	Carcinoma of uterus; metastases in femur and pelvic bones	5.04
17	M.	50	Epidermoid carcinoma involving scrotum and mons pubis	5.30
22	M.	53	Syphilis; early pulmonary tuberculosis	4.64
23	M.	54	Alcoholism	5.24
27	M.	62	Cataract	5.30
39	F.	51	Carcinoma of breast; metastases in lungs	5.40
43	M.	29	Chronic pulmonary tuberculosis	5.00
44	M.	51	Multiple sinuses of perineum, probably tuberculous	4.50
46	F.	40	Pregnant three months; syphilis; gonorrhea	5.10
61	M.	72	Autopsy: Acute colitis	4.70
66	M.	26	G. c. urethritis	5.10
67	M.	84	Arteriosclerosis; inguinal hernia	5.20
72	M.	34	Chronic arthritis	5.00
83	F.	80	Autopsy: Confluent bronchopneumonia	4.90
87	M.	..	Alcoholism	4.90
90	M.	36	Advanced pulmonary tuberculosis	4.70
91	M.	41	Syphilis; secondaries	4.50
95	M.	52	Perinephritic abscess of many months' duration	5.10
102	F.	71	Autopsy: Scirrhous carcinoma of breast; axillary lymph nodes involved	5.10
106	F.	28	Pregnant eight months	4.70
107	M.	36	Chronic pulmonary tuberculosis	4.60
109	M.	79	Cerebral hemorrhage terminating in death	4.60
111	F.	69	Syphilis; catarrhal jaundice	4.90
119	M.	65	Pulmonary tuberculosis; pleural effusion	4.50
120	F.	23	Pregnant eight months	4.80
124	M.	54	Acute miliary tuberculosis	4.50

RANGE OF SEDIMENTATION RATES.



Columns define upper and lower limits of readings in various conditions. Dark transverse lines indicate the average for each group.

results are consistent with the findings of many foreign investigators. Apparently increase in blood fibrinogen associated with tissue destruction is the most important factor determining the increased sinking rate of the red cells, according to the work of Fahraeus,¹ Levinson,⁴ and others. In our cases certainly the rate has been

TABLE III.—CASES SHOWING SEDIMENTATION RATES OF 5.5 TO 8 CC IN FIRST HOUR.

Case No.	Sex.	Age.	Chief clinical and pathological findings.	No. cc red cells sedimenting in first hour.
1	M.	68	Arteriosclerosis; varicose veins	6.75
2	F.	66	Arteriosclerosis; old hemiplegia	5.70
3	F.	76	Hypertension	6.10
4	M.	..	Hypertension	6.53
5	M.	63	Hypertension; varicose veins	6.16
6	M.	71	Glaucoma; mitral regurgitation	7.44
11	F.	28	Pregnant four months	6.44
12	F.	29	Pregnant five months	7.52
16	M.	74	Obstruction of sigmoid; carcinoma	7.50
20	M.	73	Undetermined laryngeal condition	6.95
25	M.	58	Carbuncle of neck; healed tuberculosis	5.72
28	M.	61	Arteriosclerosis	7.90
30	M.	38	Alcoholism; varicose veins	7.10
36	M.	66	Chronic pulmonary tuberculosis	5.90
38	M.	64	Kipphosis; tuberculosis of hip and elbow, healed	6.90
40	M.	66	Autopsy: Chronic myocarditis	6.50
45	F.	25	Early pregnancy	6.00
48	F.	23	Pregnant six months	6.10
49	F.	23	Healthy	7.80
51	M.	65	Arteriosclerosis; chronic arthritis	7.10
52	M.	59	Varicose veins; chronic bronchitis	7.90
53	M.	60	Varicose veins	6.10
54	M.	57	Scoliosis	7.80
55	M.	71	Hypertrophic arthritis	7.70
58	F.	71	Chronic nephritis	7.40
68	M.	16	Chronic endocarditis; rheumatic	6.90
69	M.	47	Paralysis agitans	6.20
70	M.	81	Arteriosclerosis	5.90
77	M.	65	Arteriosclerosis	7.90
79	M.	76	Ununited fracture	6.30
81	F.	55	Chronic nephritis	6.10
82	M.	26	Syphilis	6.60
85	M.	55	Auricular fibrillation	7.10
92	M.	52	Syphilis; old hemiplegia	7.60
97	M.	63	Healed tuberculosis; hernia	7.40
98	M.	45	Diabetes	7.60
104	F.	69	Chronic arthritis	7.00
105	F.	69	Paget's disease of breast	6.70
112	F.	59	Diabetes; old hemiplegia	7.50
113	F.	83	Chronic arthritis; diabetes	6.60
114	M.	..	Diabetes	6.30
115	M.	80	Diabetes; old hemiplegia	6.60
116	M.	41	Amyotrophic lateral sclerosis	7.60
117	F.	29	Pregnant six months	6.20
122	M.	61	Carcinoma of cardia; metastases in liver and lungs (autopsy)	5.60

nearly proportional to the amount of tissue destruction resulting from tumor or inflammatory exudate, cases of scirrhous carcinoma of the breast giving relatively slow rates, while highly invasive or ulcerating tumors though small in size have given high rates, and low-grade widespread inflammatory processes giving much slower rates than a smaller but more destructive inflammatory lesion. Likewise our determinations of plasma fibrinogen in these cases have in general shown high values of fibrinogen coincident with increased rate of sedimentation. Patients having marked decrease in number of red cells tend to have more rapid rates, but this factor of cell volume was found to be less important than might be supposed.

TABLE IV.—CASES SHOWING SEDIMENTATION RATES OF 8.0 TO 9.8 CC IN FIRST HOUR.

Case No.	Sex.	Age.	Chief clinical and pathological findings.	No. cc red cells sedimenting in first hour.
7	F.	31	Healthy	8.00
8	M.	29	Healthy	9.80
9	F.	26	Healthy	8.48
15	F.	68	Fibroid of uterus; old hemiplegia	8.00
24	M.	24	Fistula in ano	9.00
26	M.	56	Alcoholism	9.51
29	M.	..	Healthy	8.70
31	M.	63	Paralysis agitans	9.00
32	M.	22	Syphilis; primary lesion	8.00
34	F.	22	Postpartum one month	8.20
50	F.	35	Healthy	8.70
56	M.	49	Healthy	8.70
57	M.	33	Healthy	9.10
59	M.	35	Healthy	9.10
62	M.	82	Hernia	8.00
63	M.	51	Varicose veins	8.00
73	M.	30	Chronic urethritis	8.70
74	M.	22	Gonorrheal urethritis	8.90
75	M.	49	Transverse myelitis	8.10
76	M.	71	C. N. S. lues	8.00
78	M.	46	Tabes	8.30
80	F.	28	Healthy	8.50
86	M.	58	Hernia	9.10
88	M.	60	Spastic paraplegia	8.70
99	M.	30	Renal calculus	8.10
118	M.	27	Hernia	8.10

Discussion. The fact that there is no sharp demarkation in sedimentation rate between normal and pathological cases indicates the limitations of usefulness of this test. Apparently the difference in rate between different people, irrespective of pathological conditions, is great, and numerous factors enter into the phenomenon even in health, such as the physical and chemical conditions of the

blood, volume relations of cells and plasma, and physiological variations in the individual. For any one person, repeated determinations over a long period of time indicate that the rate is nearly a constant quantity, altered only slightly under physiological conditions, being slightly accelerated during menstruation, and tending to be slightly more rapid in women than in men, and less rapid in children than in adults.

This test is in no sense a specific one for tuberculosis, tumor, or any other condition, and it is not justifiable to lay stress upon small variations. However, it seems to be of definite value in diagnosis and prognosis, if it is used, like a blood count and other laboratory tests as an aid, to be used in conjunction with other procedures. It would seem to be of particular usefulness to apply the test to the same individual at different times during the course of an infection or the progress of a tumor, since, the rate in a normal person being almost a constant value, when in the course of a disease the rate becomes more rapid, it is definitely due to an increase in the pathological condition.

Summary. A simple method is described for determining the sedimentation rate of erythrocytes.

There is an increased rate associated with pregnancy, malignant tumors, tuberculosis, and acute inflammatory conditions.

In pathological conditions where there is an increased rate of sedimentation, the rate bears a relation to the amount of tissue destruction.

The test is advocated as an aid in diagnosis and prognosis when used in conjunction with other procedures.

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BLOOD-SUGAR RETENTION IN CARCINOMA.*

BY THOMAS C. KELLY, A.M., M.D.,

ASSOCIATE IN MEDICINE, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA.

NEARLY forty years ago, Freund,¹ in examining the blood of patients suffering from carcinoma, pointed out that, in nearly all

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such cases, there was present a hyperglycemia, and concluded that such a finding in the blood was more or less evidence of that disease.

Five years later, Trinkler,² in analyzing the blood sugar in 109 cases, comprising various diseases, concluded "that the blood of cancer patients shows in general a relatively large percentage of reducing substances, particularly glucose, and that the carcinomatous diseases of the inner organs, show a larger quantitative increase in blood-sugar concentration, than do cancers of the skin and mucosa."

Matrai³ however, reporting about the same time as Freund, maintained that such a hyperglycemia was not so much characteristic of cancer, as it was of the secondary anemia which accompanied the disease.

With the advent in recent years of more refined methods of laboratory investigation, the blood properly became a fertile field for the qualitative and quantitative estimation of various products of metabolism, both as an aid to diagnosis, and also as a means of prognosticating the future in known diseases. It was but natural therefore, that attempts were made to determine the behavior of the concentration of the sugar in the blood after the administration of a definite amount of glucose, not only in health, but also in those diseases supposedly associated with an initial hyperglycemia.

Jacobson,⁴ among the first to recognize the importance of such investigations, observed, in 14 normal persons, that, after the oral administration of 100 gm. of glucose, an increase in blood sugar occurred within five minutes, reached its height in thirty minutes, and then declined to its normal level, usually in two hours.

Hopkins,⁵ Hamman and Hirschmann⁶ with approximately the same technic, found practically similar results in health, and also observed that there was a more or less distinctive curve of hyperglycemia in certain diseases, such as diabetes, carcinoma, nephritis, various endocrine disturbances and certain infectious diseases.

Since then numerous other investigators have reported their findings with the use of what has since been known as the sugar-tolerance test. McCaskey,⁷ in an analysis of 31 cases of hyperthyroidism, found that the blood-sugar content was increased within two hours from 50 to 200 per cent. Edwards,⁸ after an analysis of 29 cases of carcinoma, concluded that the test seemed to have greater value in eliminating cancer, than in proving its existence. Rohdenburg, Bernhard and Krehbiel,⁹ who in the more recent of their two communications, made an elaborate study of sugar mobilization bases on 228 cases of numerous diseases, and concluded (a modification of their earlier view) "that there is no fixed type of reaction even in metabolic disturbances, absolutely similar curves being found in conditions as widely different as diabetes, tuberculosis, epithelioma and pregnancy." Langston,¹⁰ in an analysis of 154 patients, of whom 53 had carcinoma, in his list of conclusions,

says that "carbohydrate metabolism is disturbed by carcinomatous growth, apparently in the same way as in certain endocrine disturbances, and that there is no sugar-tolerance curve definitely characteristic of carcinoma; but most cases of carcinoma give a certain type of curve which is found in comparatively few other conditions, including tuberculosis, diabetes mellitus and hyperthyroidism." Spence¹¹ and Cammidge¹² also remarked on the hyperglycemia present in carcinoma, the former ascribing it to the hyperglycemia of old age, and the latter explaining it on the grounds of a faulty functioning of the endocrine glands.

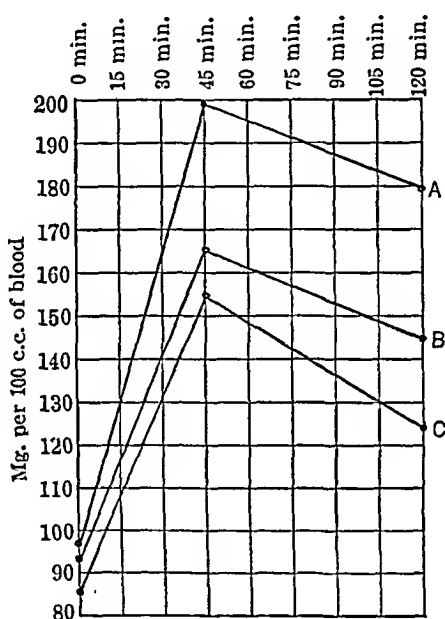
Somewhat different results were reached by Friedenwald and Grove,¹³ who, in their more recent article, conclude: "From our further study of the blood-sugar tolerance test in malignant as well as in benign diseases of the gastrointestinal tract, we are more fully convinced that the test may be utilized to great advantage as a means of differentiating between these affections, and that while it cannot in any way be considered specific for carcinoma, when taken into consideration with the other clinical evidence, it may serve as a valuable aid in diagnosis in obscure cases of carcinoma of the gastrointestinal tract."

For the past few years at the suggestion of Dr. Sailer, we have been doing the blood-sugar tolerance test on what cases seemed desirable, on our service at the Philadelphia General Hospital. The number of such reports not being sufficiently numerous to admit of any definite conclusions, I have recently investigated a series of 48 cases at the same institution, with the hope that we might arrive at more definite information as to the value of the test as a routine procedure in the aid to diagnosis of diseases of the gastrointestinal tract, as well as in suspected malignancy elsewhere in the body. Besides the cases recently examined, I have included in this report, 14 cases tested by Dr. Campion while on our service a few years ago, and 6 case reports from Dr. Sailer's service at the Presbyterian Hospital, to both of whom I wish to acknowledge my indebtedness for permission to use their results.

As such a test to be useful in general hospital practice, must be simple, I have followed the plan recommended by Rohdenburg and others, of giving in the morning, after a twelve-hour fast, 100 gm. of glucose dissolved in 300 cc of coffee, without additional sugar or cream. The blood was withdrawn from the vein just before the ingestion of glucose, again in forty-five minutes and a third specimen in two hours; the several specimens being immediately sent to the laboratory and examined under the direction of Dr. Karr, by his assistant, Miss O'Neill, to whom I am also indebted for their kindness in allowing me so suddenly to increase their already arduous duties. In the examination, the Folin-Wu method of determination of blood sugar was used.

We followed the technic of the simple administration of 100 gm. of glucose, instead of the possibly more refined use of a certain

amount of sugar per kilo of body weight, as advocated by Janney and Isaacson,¹⁴ as the latter method seemed to me to offer no additional advantages. The test, being a functional one, shows more sources of error, to my mind, in not how much is given, but how much is absorbed in a given time, and there would be no more certainty of a small, thin person absorbing, say 1.75 gm. per kilo of body weight, than there would be if the fixed amount of 100 gm. were administered. This failure to control with exactitude the absorption of any substance given by mouth, may explain the great variation in its concentration in the blood, and is a serious drawback to the dependability of the test.



A, represents the average curve of 28 cases of carcinoma of the gastrointestinal tract. B, represents the average curve of 37 cases of carcinoma elsewhere in the body. C, represents the average curve of 14 cases of various other diseases.

In the whole series of 79 cases upon which this report is based, there were 28 cases of carcinoma of the gastrointestinal tract, of whom 11 were proven either by autopsy or at the time of operation, and the remaining 17 suggestively so by the positive roentgen-ray and clinical findings. There were 37 cases of carcinoma involving portions of the body other than the gastrointestinal tract, which included 17 affecting the face, mouth and tongue, 4 the breasts, and 9 the male and female generative organs. The remaining 14 cases were done as opportunity offered, and comprised a few of arthritis and arteriosclerosis, and 6 of tuberculosis, one of which involved the intestines.

Reviewing the cases of carcinoma of the gastrointestinal tract alone, of which, as I have mentioned, there were 28, one is immediately surprised with the low fasting estimation of blood sugar—the average being 98 mg. per 100 cc of blood, and with only 6 cases, showing a reading of over 110 mg. per 100 cc. Parenthetically this

was true also of a large series of cases of carcinoma of the stomach occurring over a period of several years having only a single estimation of the blood sugar recorded—at least 75 per cent of whom were well within the normal limits. The average curve of the 28 cases referred to, showed a reading of 98 mg. fasting, 196 mg. in forty-five minutes and 179 mg. per 100 cc of blood at the end of one hundred and twenty minutes, a curve which taken as a whole is quite suggestive and in keeping with the findings of Friedenwald and Grove. The individual cases however showed considerable variation, so marked that one wonders at the possible solution. It was apparent early in our investigations, that a fact which I always believed might have some possible influence on the degree of hyperglycemia, namely, the degree of cachexia, played very little part, as the case with the greatest response to the test was one in which the patient had a large mass in the epigastrium with attachment to the left lobe of the liver, in whom there was only moderate cachexia, and a man who was extremely emaciated, with a hemoglobin of 37 per cent, had a response of 93 mg., 150 mg., and 125 mg. per 100 cc, at the three different periods of the curve. So too, the amount of involvement of the carcinomatous process seemed to have little influence, as one of the cases with little involvement of the stomach had a marked hyperglycemia, and another examined about the same time, with marked involvement of the liver, gall-bladder, esophagus and stomach, showed a response well within the supposed normal limits. The degree of involvement of the kidney at the time of the test was not sufficiently investigated to draw any definite conclusions, as measured in terms of the examination of the urine, it was apparently of no significance, those with a marked sustained hyperglycemia, for the most part showing no signs of nephritis. The average age for all the cases of carcinoma was fifty-nine years; of the ones involving the gastrointestinal tract there were 21 males and 4 females and 23 whites and 2 blacks; the other cases of carcinoma were almost equally distributed between the sexes, with the same high preponderance of the white over the colored race.

In considering the cases of carcinoma involving other portions of the body than the gastrointestinal tract, we are again amazed at the great variation in the response to the test. In this series there were 37 cases, with an average curve of 95 mg., 164 mg. and 146 mg. per 100 cc at the three periods of examination, a curve lower in all its components than that found in cases of involvement of the gastrointestinal tract, but showing in a lower degree the same general tendencies. Here, also one could not gauge the degree of hyperglycemia, either by the extent of the disease, by its situation or by the condition of the patient. There were 4 cases of carcinoma of the cervix, 2 of whom had a history of bleeding apparently relieved by radiation, but in only one was there a suggestive curve of hyperglycemia.

Of the remaining 14 cases of diseases other than carcinoma, the average curve was 84 mg., 154 mg., and 125 mg. per 100 cc of blood, showing a still lower reading than the average of the two previous series of the carcinomas, but here also was there the same general tendency to a return to the normal level within the 120-minute period. In this series there was 1 case of arthritis deformans, which showed a response to the glucose administration of 80 mg., 240 mg., 220 mg and 160 mg. per 100 cc of blood, a curve supposedly typical of carcinoma, and also one of a chronic ulcerative process of the leg, which gave a marked increase of the concentration at the end of forty-five minutes, and a still higher reading at the end of two hours. In this group there were 6 cases of tuberculosis, 1 with involvement of the intestines and the remaining 5 affecting to a marked degree the lungs. The average curve for the entire number was 87 mg., 131 mg., and 117 mg. per 100 cc of blood—figures which, if allowing of any conclusion, would indicate very little sugar retention.

Of the whole number of 65 cases of carcinoma, in spite of the high concentration of sugar in the blood, glycosuria was present in only 4 cases, in all of whom there was a concentration of sugar in the blood of 200 mg. or over, per 100 cc, at the end of the 45-minute period.

Rearranging our cases and dividing them into the three groups or types followed by Rohdenburg, Friedenwald and their co-workers, we again find some variation from their published results. In this classification, in Type I, the blood sugar at the end of the 45-minute interval, rises above the zero-hour figure, and at the end of the 120-minute interval is as high or higher than at the 45-minute interval. In Type II, the rise in the 45-minute interval occurs as in Type I, but at the 120-minute interval the curve falls almost or completely to the original figure. In Type III, the initial sugar concentration is higher than or the same as that at 45-minutes, and the 120-minute interval shows a return to the original figure more or less completely, sometimes going even higher. Classifying our cases according to these three types, we find:

	Type I.	Type II.	Type III.
Carcinoma of gastro-intestinal tract;			
28 cases	13 (46.4%)	11 (39.3%)	4 (14.3%)
Carcinoma elsewhere:			
37 cases	16 (43.2%)	21 (56.8%)	
Other diseases:			
14 cases	4 (28.6%)	9 (64.3%)	1 (7.1%)

The cause of the delayed tolerance curve or altered metabolism in cancer is still somewhat obscure. Besides the various suggestions offered in the beginning of this paper, two possibilities have been made by Dr. Charles E. Simon. One is that it is caused by the increased demand of the growing tumor for carbohydrates, and the second, that a hormone is liberated by the carcinoma, thus impairing the power of the tissues to oxidize sugar. A third possibility is

that suggested by Langston, "that a specific hormone is liberated by the carcinoma cells, which acts to accelerate the process of glycogenolysis, or retard the process of glycogenolysis, or both, either directly, or by acting upon one or more of the endocrine organs or the vegetative nervous system."

Summary. In view of the great variation in the individual records of our cases, I am still unable to arrive at any satisfactory conclusion as to the value of the sugar-tolerance test as a routine help in the clinical diagnosis of carcinoma. Our technic was as nearly perfect as it could be under the circumstances; the blood was withdrawn by one worker, Dr. Suravitz, who was not only very skilful in his manipulations, but extremely insistent that the specimens be examined promptly. From our observations, neither the site of the disease, the extent of the process, or the general condition of the patient, seemed to show any constant index as to the degree or duration of the concentration of sugar in the blood. It may be that the condition of health of the kidney may have some marked influence on the test, not only in carcinoma but in other diseased conditions; but in our series of cases, measured by the examination of the urine and not by the chemical analysis of the blood, the role of the kidney seemed to be unimportant.

Therefore, while patients suffering from carcinoma show an average higher degree of blood-sugar concentration than is usually the case, the great variation in the individual records, as well as the fact that equally high, if not higher responses to the oral administration of sugar, may occur in so many other conditions (focal infections, arthritis, diabetes, endocrine disturbances), leads me to conclude, that the blood-sugar tolerance test as a clinical aid in the diagnosis of cancer is of suggestive value alone, and that only when taken in conjunction with other and more positive clinical and laboratory data.

INDIVIDUAL CASE RECORDS.

	Mg. per 100 cc of blood.		
	Fasting.	45 minutes.	120 minutes.
Carcinoma of:			
Stomach	90	186	143
Stomach and esophagus	112	149	180
Stomach	90	240	200
Rectum with metastasis to liver	95	135	135
Stomach and liver	95	190	140
Rectum	110	180	140
Rectum	90	100	100
Stomach and liver	65	200	150
Stomach	128	385	290
Stomach	93	150	125
Stomach	105	445	445
Stomach and esophagus	121	200	250
Stomach (general abdominal)	111	250	210
Stomach	64	186	187
Stomach	105	160	125
Stomach	130	210	169
Stomach	75	340	300
Stomach	120	250	160

	Mg. per 100 cc of blood.		
	Fasting.	45 minutes.	120 minutes.
Carcinoma of:			
Stomach	105	110	165
Stomach	95	120	185
Stomach	75	120	125
Stomach	75	200	165
Stomach	75	150	100
Stomach	110	116	180
Stomach	65	220	260
Stomach	150	210	130
Stomach	90	120	90
Rectum	95	170	166
Jaw	90	150	120
Lower lip	98	136	140
Cheek	80	180	140
Tongue and cheek	100	240	252
Nose and both cheeks	75	200	254
Nose, with pernicious anemia	98	150	140
Face and forehead	115	190	100
Lip metastasis to neck	80	150	160
Tongue and floor of mouth	85	120	80
Floor of mouth—metastasis to neck	110	178	156
Lip—infiltation of neck and jaw	86	145	118
Lip—metastasis to neck	105	160	145
Neck (parotid)—metastasis to lungs	85	220	200
Left ear and neck	110	180	150
Ear and scalp	85	150	125
Scalp	90	196	150
Pharynx	94	194	160
Orbit	100	125	125
Breast	80	120	90
Breast	138	265	170
Breast	93	135	130
Breast	95	134	130
Breast	90	150	155
Cervix	100	145	120
Cervix	87	140	130
Cervix	120	260	220
Cervix	90	120	105
Uterus	145	260	150
Bladder and prostate	75	135	140
Penis	95	110	125
Testicle	80	95	120
Prostate	110	140	148
Leg (pathological report)	95	220	200
Sarcoma of:			
Tibia	85	150	100
Ankle (angiosarcoma)	100	150	180
Lymphosarcoma	93	180	190
Fibrosarcoma of thigh	93	100	100
Frolich's syndrome	92	180	100
Chronic inflammatory ulcer of leg	100	180	175
Tuberculosis of intestines	100	140	140
Pulmonary tuberculosis and enteritis	85	110	140
Pulmonary tuberculosis and laryngitis	90	115	110
Pulmonary tuberculosis	65	120	75
Pulmonary tuberculosis	90	135	110
Pulmonary tuberculosis	85	165	125
Chronic ethmoiditis	62	146	140
Arteriosclerosis	80	140	120
Arthritis deformans	80	240	220
Arteriosclerosis	75	120	110
Arthritis and arteriosclerosis	80	178	100
Senility	85	60	90

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A DISCUSSION OF THE CLINICAL AND LABORATORY CLINICAL FINDINGS IN CERTAIN CASES OF OBSTRUCTION IN THE UPPER GASTROINTESTINAL TRACT.*

THE RÔLE OF BLOOD CHEMISTRY IN DIAGNOSIS, PROGNOSIS AND TREATMENT OF THIS CONDITION.

BY CHARLES S. McVICAR, M.D.,

DIVISION OF MEDICINE, MAYO CLINIC, ROCHESTER, MINNESOTA.

THE clinical importance of gross disturbances of motor function of the upper gastrointestinal tract is well established. Interruption of this function may be due to obstruction by malignant or inflammatory infiltrations, or to exhaustion (decompensation) of the muscle above organic lesions which only partly occlude. It may follow operations such as gastroenterostomy. When stasis occurs postoperatively, it may be due to mechanical obstruction such as the kinking of one or both loops of the jejunum. Not infrequently stasis appears to be due to a temporary paresis of the muscular tube, and after a longer or shorter refractory period, function is restored. The prognostic significance of stasis has been emphasized by Berkman,¹ who has shown that appropriate preoperative care, directed to cleansing lavage of the stomach, allowing a reasonable time for the recovery of muscle tone, and the restoration of a positive water balance, has led to a remarkable lowering of operative mortality. Simple measures suffice for the majority of cases. Intensive study has revealed a group showing more profound disturbance, and the studies here reported have to do with the clinical and laboratory investigation of the cases of severe toxemia.

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An historical and critical review of the experimental work on high intestinal obstruction has been made by Ellis.⁴ Mayo Robson¹⁶ credits Morgagni with the first reference to tetanoid symptoms occurring with diseases of the stomach. Kussmaul¹² gave the first clinical description of gastric tetany. Until quite recently, clinical descriptions of severe toxemia in cases of obstruction have appeared under the title of "gastric tetany." As a rule, the organic lesion associated has been at or just above or below the pylorus, where most organic lesions of the upper gastrointestinal tract occur. Mayo Robson describes a fatal case of stasis with tetany, in which a dilatation of the small intestine to the middle of the jejunum was found at necropsy. Below this point, the gut was collapsed, although no actual obstruction could be found, and he suggests the possibility of paralytic ileus as the cause of the symptoms. Rodman¹⁷ describes a case in which tetany appeared on the eleventh day after a gastroenterostomy had been made for duodenal ulcer; the patient recovered.

In 1914, Tileston and Comfort¹⁸ found a high non-protein nitrogen in the blood in cases of intestinal obstruction in animals. In 1915, Wilson¹⁹ and his associates reported high alveolar carbon dioxide tension in tetany following parathyroidectomy in dogs. McCann¹⁴ showed that, in cases of pyloric closure, the alkaline reserve of the blood increased rapidly until death. In 1920, McCallum¹³ found that pyloric occlusion in dogs resulted in a marked fall in the plasma chlorids. Hastings, Murray, and Murray¹¹ confirmed the findings of a high plasma carbon dioxide combining power, and of a striking fall in the plasma chlorids in dogs subjected to pyloric closure. These important laboratory findings, namely, high non-protein nitrogen, high carbon dioxide combining power of the plasma and low blood chlorids, have been reported by Haden and Orr^{5, 10} in 3 patients who developed acute symptoms following gastroenterostomy. Murray¹⁵ reports the same findings in 5 patients with organic obstruction at the pylorus. He emphasizes vomiting as a factor in producing the disturbance in the acid base equilibrium. Brown, Eusterman, Hartman, and Rowntree² report 11 cases from the Mayo Clinic in which marked toxemia occurring with upper intestinal stasis, showed characteristic changes in the laboratory findings. They have defined the clinical picture as characterized by (1) vomiting, (2) evidences of dehydration, (3) tetany-like manifestations, and (4) features of shock and uremia. They stressed the definite evidence of renal damage in these cases and have made suggestions for treatment. Haden and Orr have reported 4 additional cases of acute intestinal stasis in which the organic cause for the ileus was situated in the lower ileum. They found a sharp fall in the blood chlorids, a rise in the non-protein nitrogen, and a tendency to a rise in the carbon dioxide combining power of the plasma. They believe the fall in chlorids to be the primary change, and take this as an indication for using sodium chlorid as a remedy.

The use of sodium chlorid as a therapeutic agent had a firm basis in the experimental work of McCallum, who found that he could postpone death and prevent the evidences of tetany in dogs with pyloric occlusion by the intravenous use of sodium chlorid. Dixon³ reports from the Mayo Clinic 6 cases of toxemia of high intestinal stasis treated with success, or with marked improvement by the administration of sodium chlorid.

CASE I (A447373).—A man, aged sixty-one years, registered at the Clinic November 13, 1923. He was markedly prostrated, dehydrated, and emaciated. His skin was dry, cherry red in tint in the ears, cheeks and nose. There was marked oral sepsis. The facial muscles and fingers twitched. The systolic blood-pressure was 100, the diastolic 75. He was semiconscious, and incoherent; his condition resembled typhoid. There was gastric succussion, frequent left to right epigastric peristalsis, and scanty urine with incontinence of sphincters. The onset of epigastric distress had occurred about three years before, and had been diagnosed duodenal ulcer with obstruction. Medical treatment afforded relief. In 1921 and 1922 the condition recurred, and distress and vomiting were severe. This was again relieved by intensive medical treatment. The last attack had occurred about five months before. There were no remissions; the condition was progressive; coffee-ground material was vomited occasionally. Fifty pounds in weight had been lost during these five months. The patient had taken no food and only a restricted amount of fluid for three weeks. Gastroenterostomy was performed November 20, and an obstructive duodenal ulcer was found at the upper border of the duodenum, just below the pylorus. The patient's convalescence was uneventful, and he was dismissed from the hospital December 5.

TABLE I.—SEVERE TOXEMIA WITH ORGANIC OBSTRUCTION.

Date, 1923.	Blood urea, mg. for each 100 cc.	Plasma chlorides, mg. for each 100 cc.	Plasma carbon dioxide combining power, volume per cent.	Blood-pressure.	Phenol-sulphone-phthalein, per cent.	Hemoglobin.
Normal	26	560 to 650	56 to 65			
Nov. 13	303	367	78	100/75		
Nov. 14	298	355	89			
Nov. 15	234	380	89	100/68	80
Nov. 16	226	450	88	110/70	86
Nov. 17	162	500	130/70	55
Nov. 19	51	560	68			
Nov. 20	Operation	35	
Nov. 21	43	590	58	38	69
Nov. 26	27	525	70	45	64
Nov. 29	555	67	112/68	43	
Dec. 10	21	590	62	70

Table I outlines the clinical appearance, course and laboratory findings in a severe case of toxemia. Evidence of shock, dehydra-

tion and symptoms suggesting uremia predominate. The high color of the skin in the early stages was probably due to blood concentration. Dilution of the blood and subsequent readjustment is shown in the hemoglobin readings. The urea, chlorid and carbon dioxid values are characteristic. Clinical improvement coincided with a return toward normal values. Treatment of the underlying cause of the illness was surgical, but the operative risk was very appreciably lessened by special preoperative management. Table II illustrates the insidious onset in a postoperative case. Although large quantities of secretion were vomited on two occasions, there was nothing alarming about the patient's appearance until the onset of tetany. Blood examination then revealed the severity of the toxemia. Study of the blood chemistry affords a more precise means of measuring severity than the clinical appearance. Asthenia and mental confusion were again suggestive of uremia. The degree of renal involvement is seen in the failure of phenolsulphonephthalein excretion in the early stages. It may be difficult in severe cases to estimate the phenolsulphonephthalein excretion because of temporary suppression of urine, or because of incontinence. The demand of the organism for salt is indicated in the diminished output of sodium chlorid in the urine as compared with the intake. Cough and respiratory embarrassment on the third day of observation suggested the possible danger of edema of the lungs from forcing fluids. Table III shows a mild case of toxemia. The early examination of the blood in suspected cases will result in early recognition and early treatment. If during treatment, blood chemistry readings cease to improve or swing back toward extreme values, mechanical obstruction is probable, and surgical exploration is indicated. In Table IV are tabulated in chronologic sequence the findings in 30 cases recognized as toxemia due to high intestinal stasis, since the application of the laboratory investigations mentioned. Only cases in which there are extreme values for urca, chlorids, and carbon dioxid, are given. In all cases in which studies were made, at least two and usually all three readings showed abnormal values. It is significant that early cases were diagnosed on the clinical evidence of tetany. The yearly incidence of tetany in our experience, is about the same: 3 cases in 1920, 2 cases in 1921, 3 cases in 1922, and 3 cases in 1923; whereas 12 cases of toxemia were diagnosed in 1923, and 7 cases in 1924 up to April 30. It will be seen that tetany may occur with relatively mild disturbance of urea and chlorid readings (Case 29). The incidence of tetany is apparently closely related to the increased carbon dioxid combining power (alkali reserve) of the plasma. One apparent exception to this tendency occurs in Case 10, but the reading for carbon dioxid was not made until two days after the occurrence and treatment of tetany. In Case 13, the extremely high value, 161 volumes per cent for plasma carbon dioxid without tetany has not been explained; this is our

only exception to the rule that tetany is associated with a condition of alkalosis. Tetany should be regarded merely as a possible incident in the course of the toxemia, and although always of serious prognostic significance, the absence of tetany must not be interpreted as an evidence of a mild degree of toxemia.

Tetany, as the term is used here, is a state in which spontaneous painful spasms of the hands occur with the production of the "accoucheur's hand," or in which this phenomenon could be induced by pressure on the nerves of the upper arm with the cuff of a blood-pressure apparatus (Trousseau's sign). Possibly routine measurement of the neuromuscular response to electric stimulation would reveal additional cases with increased irritability. It is difficult to be sure that twitching of the facial muscles is, or is not, evidence of tetany in cases in which uremia is threatening. Table V helps to visualize the possible mechanism of tetany. In infantile tetany, in the tetany which follows removal of the parathyroid glands, and in the tetany occurring in association with severe diarrhea, for example, in sprue, a low calcium content of the blood serum has been found. Tetany in these cases has been explained as an imbalance between the monovalent and divalent cations; the ratio may be expressed in terms of milligrams of each substance in 100 cc of blood serum, thus:

$$\frac{\text{Na (337.5)} + \text{K (22.5)}}{\text{Ca (10)} + \text{Mg (2)}} = \frac{360}{12} = \frac{30}{1} \text{ which is the normal ratio.}$$

Tetany is likely to occur if the ratio becomes $\frac{40}{1}$.

The only variant so far noted is calcium. If calcium is reduced to 7 mg. for each 100 cc, tetany usually occurs, that is,

$$\frac{337.5 + 22.5}{7 + 2} = \frac{360}{9} = \frac{40}{1}.$$

It is conceivable that the same resulting ratio might be attained by a sufficient increase in the numerator of the fraction, that is, by increasing the quantity of sodium or potassium, or both, in the blood serum. Therefore, the concentration of the sodium, potassium, calcium and magnesium in the serum of patients presenting the characteristic laboratory and clinical evidence of toxemia of high intestinal obstruction has been studied.

CASE II (A445013).—A man, aged forty-five years, registered at the clinic October 19, 1923. A posterior gastroenterostomy for penetrating duodenal ulcer which was adherent to the gallbladder, and an appendectomy for chronic inflammation of appendix were performed October 24. Nine days after the operation the patient vomited 1000 cc of fluid, and fourteen days after operation, he vomited 1400 cc. On the nineteenth day he complained of cramping in the hands. Trousseau and Chvostek signs were positive.

TABLE II.—SEVERE TOXEMIA WITH TETANY AFTER OPERATION.

Date, 1923.	Intake, cc.	Urine, cc.	Emesis, cc.	Sodium chlorid, gm.		Phenolsulphone-phthalein, per cent.	Blood-pressure.	Blood chemistry.			Remarks.
				Intake.	Urine output.			Blood urea, mg. for each 100 cc.	Plasma chlorides, mg. for each 100 cc.	Plasma carbon dioxide, volume, per cent.	
Nov. 11	3800	0	0	12.6	282	271	109	Tetany.
Nov. 12	4400	700	0	20.3	140/50	316	350	86	Confused; cough; waterlogged?
Nov. 13	2400	1970	0	0	115/70	297	384	77	Asthenia.
Nov. 14	3125	2200	1560	10.0	98/60	288	420	70	Prostrations, 3.
Nov. 15	3000	2500	0	6.5	2.1	..	95/50	Clear mentally.
Nov. 16	2500	2840	0	12.0	1.5	..	108/62	190	485	66	Improved.
Nov. 17	3510	3245	0	8.0	...	0	102/62	Up one-half hour.
Nov. 18	3580	2990	0	10.0	3.1	..	114/56	Steady improvement.
Nov. 19	3840	3370	0	10.0	3.4	25	86	570	52	
Nov. 20	3540	3570	0	3.0	4.8	15	
Nov. 21	...	3000	0	Diet	4.6	54	
Nov. 22	...	2900	0	Diet	7.1	25				
Nov. 23	...	2600	0	Diet	5.2	30				
Nov. 26	...	2300	0	Diet	5.2				
Nov. 27	...	2300	0	Diet	7.2	37	27	605	55	Very hungry.
Dec. 1				

CASE III (A453287).—A woman, aged fifty-two years, registered at the Clinic January 21, 1924. She gave a history of having had peptic ulcer type of dyspepsia with progressive increase in severity of distress during "spells," and progressive shortening of the intervals of freedom. A clinical diagnosis of peptic ulcer was confirmed by the roentgen-ray findings of deformity of the duodenal bulb. The specific gravity of the urine was 1.015; there was no albumin and no sugar. The phenolsulphonephthalein return was 35 per cent; the systolic blood-pressure was 160, the diastolic 90. The test-meal revealed total acidity 50, free hydrochloric acid, 36; quantity 100 cc. Posterior gastroenterostomy and appendectomy were performed February 16. The contracting duodenal ulcer was found 2 cm. below the pylorus, producing definite destruction in the duodenum. The appendix contained a number of large fecoliths. The stomach was small and it was impracticable to make the gastroenterostomy as large as usual. The possibility of postoperative retention, until edema around the gastroenterostomy had subsided, was anticipated. Fluids were supplied by subcutaneous sodium chlorid solution; sodium chlorid was given by mouth. The patient was dismissed from observation March 5.

TABLE III.—MILD TOXEMIA AFTER OPERATION.

Date, 1923.	Recovered by gastric lavage, cc.	Blood urea, mg. for each 100 cc.	Plasma carbon dioxide combining power, volume per cent.	Plasma chlorids as sodium chlorid, mg. for each 100 cc.	Sodium chlorid as salol coated tablets, gm.
Normal	26	56 to 65	560 to 650	
Feb. 16	Operation			
Feb. 17	300				
Feb. 18	550				
Feb. 19	700				
Feb. 20	800				
Feb. 21	300	90	76	470	
Feb. 22	300	87	74	450	15
Feb. 23	50	74	470	15
Feb. 24	15
Feb. 25	34	70	500	15
Feb. 26	35	77	570	
Feb. 28	18	53	614	
Mar. 5	Dismissed	from hospital			

Before considering the results of this study, attention is again directed to Table V, which shows that tetany may occur when an imbalance is induced between the bicarbonate, the free alkali of the blood serum, and the free carbonic acid. Actually tetany has followed excessive feeding of sodium bicarbonate, when the numerator of the fraction $\frac{\text{BHCO}_3}{\text{H}_2\text{CO}_3}$ is increased, that is $\frac{1+}{1}$. It has also followed forced breathing which has abstracted the acid carbon dioxide from the blood, when the denominator of the fraction has been reduced, that is, $\frac{1}{1-}$. There is some evidence that antagonism

in respect to effect on neuromuscular irritability is not confined to basic ions, but that the anions may also participate in the maintenance of equilibrium. It is established in physiology that, calcium and magnesium salts are sedative, and it is also established that the sedative effects of certain coal tar derivatives vary proportionately with the effect of the chlorid ions present (Rudolf). The occurrence of low plasma chlorids in cases of tetany suggested a possible mechanism for tetany (Table V). In such a grouping, equilibrium would be said to exist, not between acid and base, or between different classes of cations, but in a formula which may be expressed irritating cations + irritating anions. Accordingly, with a low sedative cations + sedative anions chlorid content of the blood serum, imbalance might be the result of diminution of the denominator. This suggestion cannot be harmonized with the findings in Table IV which seem to show that the occurrence of tetany is determined by a condition of alkalosis. Nevertheless, chlorin may act to inhibit tetany, and there is increasing clinical evidence of a relationship between the plasma chlorid content and the alkali reserve.

TABLE IV.—SURVEY IN CASES OF TOXEMIA IN HIGH INTESTINAL OBSTRUCTION AT THE MAYO CLINIC, MAY, 1920 TO MAY, 1924.

Case.	Date of registration.	Blood urea, mg. for each 100 cc.	Plasma chlorids, mg. for each 100 cc.	Plasma carbon dioxid, volume per cent.	Remarks.
Normal		26	560 to 650	56 to 65	
1 A91674	May 17, 1920	120	Tetany.
2 A317395	May 27, 1920	No study	Tetany.
3 A333574	Sept. 11, 1920	124	158	Tetany.
4 A353616	Mar. 28, 1921	110	Tetany.
5 A367874	Aug. 9, 1921	88	105	Tetany.
6 A369991	Aug. 26, 1921	403	240	98	
7 A297046	Sept. 25, 1921	226	485	86	
8 A108879	Jan. 28, 1922	31	428	98	
9 A382714	Feb. 1, 1922	235	353	125	Tetany.
10 A383808	Feb. 10, 1922	192	320	84	Tetany.
11 A413425	Dec. 25, 1922	88	375	163	Tetany.
12 A414392	Jan. 10, 1923	103	Tetany.
13 A424454	May 5, 1923	126	495	161	
14 A426694	May 24, 1923	86	450	82	
15 A430948	June 26, 1923	200	450	108	Tetany.
16 A430537	June 26, 1923	54	450	83	
17 A445013	Oct. 19, 1923	316	271	109	Tetany.
18 A447373	Nov. 13, 1923	303	355	89	
19 A447960	Nov. 19, 1923	22	435	89	
20 A448907	Nov. 29, 1923	414	383	83	
21 A449440	Dec. 5, 1923	34	421	81	
22 A449776	Dec. 8, 1923	74	530	97	
23 A451343	Dec. 28, 1923	104	498	58	
24 A452013	Jan. 11, 1924	154	519	107	
25 A453329	Jan. 21, 1924	70	465	88	
26 A453287	Jan. 21, 1924	90	450	77	
27 A454709	Feb. 5, 1924	51	445	78	
28 A257819	Mar. 7, 1924	141	565	76	
29 A455114	Mar. 11, 1924	110	408	118	Tetany.
30 A462106	April 24, 1924	112	464	86	

Table VI is self explanatory. The high, low, and average content of sodium, potassium, calcium, and magnesium were determined in

eases of toxemia and in controls. The findings for sodium and magnesium are clearly within the normal. The findings for calcium are a little low, but are still well above the values which are associated with the appearance of tetany in the conditions shown in Table V. The range of potassium values is low in toxemia, but this low range was not found to be more striking in cases in which there was tetany than in cases in which there was no tetany. The clinical manifestations of toxemia, including tetany, are not associated with significant changes in the concentration in blood serum of the mineral bases.

TABLE V.—THEORIES OF TETANY.

1. Imbalance of cations.

$$\text{Normal, } \frac{\text{Na} + \text{K (irritating)}}{\text{Ca} + \text{Mg (sedative)}} = \frac{337.5 + 22.5}{10 + 2} = \frac{360}{12} = \frac{30}{1}$$

Either, increasing numerator
or decreasing denominator.

$$\text{Tetany is accompanied by low Ca values } \frac{337.5 + 22.5}{7 + 2} = \frac{360}{9} = \frac{40}{1}$$

In, infantile tetany.
tetany, parathyreopriva.
tetany, of severe diarrhea.

2. Disturbed acid base equilibrium: alkalosis.

$$\frac{\text{B H CO}_3}{\text{H}_2 \text{ CO}_3} = \frac{1}{1}$$

$$\begin{array}{l} \text{Either, increasing numerator as in excessive soda feeding } \frac{\text{B H CO}_3}{\text{H}_2 \text{ CO}_3} = \frac{1+}{1} \\ \text{or decreasing denominator as in hyperpnea } \frac{\text{B H CO}_3}{\text{H}_2 \text{ CO}_3} = \frac{1}{1-} \end{array}$$

3. Imbalance of irritating and sedative ions irrespective of whether basic or acid.

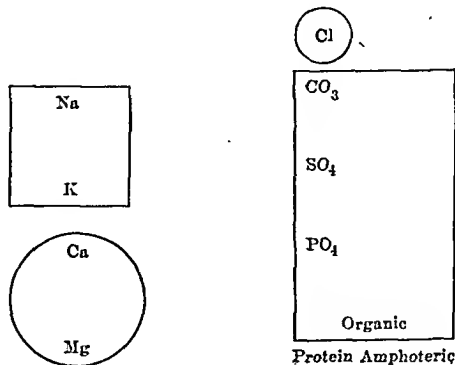


TABLE VI.—INORGANIC BASES IN BLOOD SERUM IN THE TOXEMIA OF HIGH GASTRO-INTESTINAL OBSTRUCTION AND IN OBSTRUCTION WITHOUT TOXEMIA.

	Sodium, mg. for each 100 cc.				Potassium, mg. for each 100 cc.				Calcium, mg. for each 100 cc.				Magnesium, mg. for each 100 cc.				Inorganic phosphorus, mg. for each 100 cc.			
	Observations.	High.	Low.	Average.	Observations.	High.	Low.	Average.	Observations.	High.	Low.	Average.	Observations.	High.	Low.	Average.	Observations.	High.	Low.	Average.
Normal values Kramer and Tisdall	335	20.5	10.5	2.0	2.3
High intestinal obstruction with toxemia . .	13	380	290	337	14	18.5	12.0	15.4	12	9.2	7.7	8.6	13	4.8	2.0	3.0	7	9.0	1.1	5.3
Benign obstructive lesions (ulcer) near pylorus . . .	20	385	308	343	19	24.4	16.3	19.8	20	11.0	8.5	9.9	18	3.9	2.1	2.5	17	8.5	1.5	3.4
Malignant obstructive lesions (carcinoma) near pylorus . .	11	371	319	341	11	21.6	17.8	19.1	11	10.8	8.8	9.8	11	2.6	2.2	2.4	11	4.4	2.1	3.2
Miscellaneous, malfunctioning gastro-enterostomy, carcinoma of colon, and so forth .	8	365	307	354	7	23.5	18.3	20.6	7	10.7	7.4	9.4	5	4.0	1.0	2.1	2	3.6	3.2	3.4

Treatment. The object of treating organic obstruction is to place the patient in a safer condition for surgical procedures. In postoperative ileus, an effort is made to counteract the effects of the toxemia until muscle function is restored. The progress of treatment can be measured by frequent chemical examinations of the blood.

The outstanding features suggesting treatment are dehydration, diminished output of urine, low blood-pressure, shock-like prostration, high non-protein nitrogen content of the blood, low blood chlorids, and a tendency to a high carbon dioxid combining power of the plasma. The administration of water is indicated to combat dehydration, to counteract shock, to promote diuresis, and to wash out the nitrogenous waste products.

It is not clear whether the high blood urea is evidence of excessive tissue catabolism, or of retention due to renal inadequacy, or whether both factors are involved. Certainly renal insufficiency is a factor. Sugar has been used to spare protein, and in intravenous injection to promote diuresis.

The experiments of MacCallum, and the increasing clinical experience in the Mayo Clinic, indicate that the administration of salt is desirable. There seems to be a markedly increased demand in the tissues for sodium chlorid. In spite of a liberal intake of sodium chlorid, the output of salt in the urine may be scanty, even for several days after the blood chlorids reach a normal level. It has been suggested that the lowering of blood chlorids is due to the loss of hydrochloric acid from the gastric juice by vomiting. In pyloric occlusion in rabbits that cannot vomit, however, a sharp fall in chlorids has been noted by Haden and Orr, who have also found a fall in chlorids after obstruction of the cardia. Clinically, toxemia has appeared with very little vomiting, and conversely, prolonged, frequent vomiting is not always accompanied by a fall in chlorids. Clinically, it is impracticable to administer hydrochloric acid in amounts adequate to replace that lost by vomiting or lavage, and it appears that sodium chlorid is efficient. Lavage is usually practised on the theory that the secretion contains a toxin. Lavage in functional ileus seems especially indicated because it removes a gross weight which must interfere with the recovery of tone. Lavage should anticipate vomiting in gross retentions where vomiting is exhausting to the patient.

Perhaps the most important single fact which blood chemistry studies have revealed concerning this type of toxemia is the invariable tendency toward alkalosis. The administration of alkalis is, therefore, clearly contraindicated in proved or suspected cases of toxemia, due to organic or functional obstruction in the upper gastrointestinal tract.

Summary. 1. With the toxemia of high intestinal obstruction, characteristic changes occur in the chemistry of the blood, namely,

a rise in the blood urea, a fall in the plasma chlorids, and a rise in the carbon dioxid combining power of the plasma.

2. By a study of the chemistry of the blood, the condition can be recognized early, the severity can be measured, and the progress of treatment watched.

3. No significant variation has been found in the concentration of the inorganic bases of the blood serum in this condition.

4. Tetany should be considered as a possible severe complication of the toxemia, but severe toxemia may exist without tetany.

5. Tetany may be anticipated when the carbon dioxid combining power of the plasma is found to be above 100 volumes per cent.

6. The administration of sodium chlorid, sugar, and water, has been found of value in treatment.

7. All cases show a tendency to alkalosis, and the use of alkali in treatment is contraindicated.

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DEHYDRATION IN THE NUTRITIONAL DISORDERS OF INFANCY (A CORRELATION OF CLINICAL AND LABORATORY FINDINGS).

BY A. GRAEME MITCHELL, M.D.,

AND

LEON JONAS, M.D.,*

PHILADELPHIA.

(From the Medical Service of the Children's Hospital, Philadelphia and the Chemical Division of the William Pepper Laboratory of Clinical Medicine of the University of Pennsylvania.)

DEHYDRATION occurs frequently in infants with those acute gastrointestinal disturbances that are accompanied by diarrhea of a severe nature and not uncommonly by vomiting. Certain quite characteristic symptoms follow when fluid is not supplied or retained to make up for the water lost from the body. These symptoms occur more readily if dehydration takes place in an infant whose previous nutritional state has been poor. By unsatisfactory nutrition we mean not only those extreme states of malnutrition for which Marriott prefers the term "athrepsia," but also the condition of excessive weight which often arises when carbohydrate has been fed in large amount. In both these extremes diarrhea is especially to be dreaded. These faulty nutritional states are by no means the only ones in which dehydration and its consequent symptoms may develop. Almost any condition in which fluid is taken in insufficient amount or is lost from the body will lead to somewhat similar manifestations. To be mentioned in this connection are the acute infections of the respiratory tract, intestinal obstruction and pyloric stenosis.

The symptoms to which we refer have been described by Chapin and Pease,¹ Schloss and Stetson,² Marriott³ and Schwartz and Kohn.⁴ The gastrointestinal tract, the circulatory system, the cerebrospinal system contribute to the symptomatology; there are alterations in respiration and a diminution in the output of urine. After a variable period of diarrhea, and perhaps of vomiting, the infant suddenly becomes desperately ill and toxic. There is a rapid and marked loss of weight and usually a rise in temperature. The skin is dry and may be raised from the surface of the body in folds which smooth out only after a perceptible interval. The color is slate gray and also may be slightly cyanotic. The expression is anxious and later may be vacant and staring, or the upper lids may be partly ptosed. The mucous membrane of the lips and mouth is dry and of a cherry-red hue. The fontanel is depressed.

* Read before the American Pediatric Society, June, 1924.

The pulse is rapid and of poor volume, and the hands and feet are cold and clammy. Alteration of the respiratory rate and rhythm is usually observed, the breathing being rapid and shallow or deep and sighing—typical of hyperpnea. Great restlessness and irritability are followed by stupor and coma, and at times convulsive seizures which are terminal symptoms.

The predisposing causes of this toxic state have been enumerated clearly by Schwartz and Kohn.⁴ The symptoms are preceded always by a gastrointestinal disturbance with diarrhea or vomiting or both; artificially-fed infants who have had long-continued difficulties in digestion, or who have been fed improperly, usually with high carbohydrate mixtures, are more susceptible and especially so during the summer months. It is obvious that some of these factors, such as diarrhea and vomiting and high external temperature increase water loss. A rise in external temperature from 20° to 36° C. may lead to 600 per cent increase in water elimination by the skin and lungs.⁵ The immunity of breast-fed infants points distinctly to the effect of artificial feeding.

It is notorious that infants overfed with carbohydrate for long periods are especially liable to the development of dehydration when diarrhea supervenes. Balcar, Sansum and Woodyatt⁶ have suggested that the body water exists in two forms: (1) Free and uncombined and (2) in combination with colloids. If this is true it may well be that in the hydremic tissues of these flabby infants the water is in large part uncombined. The sudden and marked loss of weight with diarrhea can only be explained by water loss.

In recent years several investigations have been made to explain the causes of the toxic state into which some of the dehydrated infants lapse. Marriott³ states: "The infant as an organic whole must be considered. The time has passed when we center our attention exclusively on the alimentary tract and allow the infant to die of a curable derangement of the intermediary metabolism."

Howland and Marriott⁷ found an acidosis when they studied the carbon-dioxide tension of the alveolar air, the hydrogen-ion concentration of the blood serum, the alkali reserve of the serum, the amount of alkali required to alter the reaction of the urine and the combining power of the hemoglobin with oxygen. They suggest the following explanation of the acidosis: "Under normal conditions the kidney excretes a very considerable quantity of acid, chiefly in the form of acid phosphate. A failure of this special function of the kidney would result in a retention of acid phosphate and a consequent acidosis. In severe diarrhea the urinary output may be markedly diminished, even to the point of complete anuria. the kidney becoming functionally more or less inactive, even though no organic changes may be present. That diminished acid excretion and consequent retention of acid phosphate in the body fluids would occur under these conditions seems probable."

Chapin and Pease¹ demonstrated an acidosis by the lowered carbon-dioxide tension of the blood. They consider the etiological factor of the acidosis to be the split products of the protein in cow's milk.

Schloss and Stetson² found the following signs of acidosis; decrease of the carbon-dioxide tension of the alveolar air and of the carbon-dioxide combining power of the blood plasma, the high ammonia coefficient in the urine, the increased tolerance to sodium bicarbonate, and the improvement of symptoms after the administration of sodium bicarbonate.

In 3 of 6 cases Minsk and Sauer³ found a definite increase of both the total non-protein nitrogen and the urea nitrogen of the blood. In another series of infants who were athreptic but not toxic the non-protein nitrogen frequently exceeded 30 mg. per 100 cc of blood (method of Folin and Denis). In the milder intestinal disorders the non-protein nitrogen and the urea nitrogen were practically normal.

Schloss⁹ determined the non-protein nitrogen, the corpuscular volume, the specific gravity and the total solids of the blood, and in a few cases its creatinin and uric acid content. The amount of urine and the phenolsulphonephthalein elimination, as well as Ambard's coefficient of urea excretion were noted. Schloss concludes: "In intestinal intoxication there is a marked increase in the non-protein nitrogen and urea of the blood. This increase is not due directly to increased concentration of the blood from loss of water, but is due to defective kidney elimination. The renal lesions in intestinal intoxication are not sufficient to account for the impaired elimination by the kidney (nine kidneys examined). It is probable that lack of water restricts the formation of urine. This condition is probably due to the following factors which may act singly or in combination: (1) The loss of water in the stools is so great that it is impossible for the infant to ingest sufficient fluid to replace the loss; (2) the patient refuses to ingest fluid or vomits practically all that is taken. As a result the tissues become dehydrated. The retention of nitrogenous waste products and the failure of the kidney to do its part in preserving the acid-base equilibrium result from deficient secretion of the urine. Oliguria may be due to the fact that the dehydrated tissues hold as much water as possible, so that none is available for the formation of urine. Other factors, dependent mainly on the loss of water, which may play a role are: (1) An increase in the concentration of blood colloids to such degree that their osmotic pressure is greater than the arterial pressure in the kidney; (2) a diminution in the total blood volume leading to decreased blood flow through the kidney. The symptoms of intestinal intoxication are essentially those of uremia. Acidosis plays a part in the symptomatology, but the essential cause is probably some unknown toxic agency."

Schwartz and Kohn⁴ in their cases examined the blood for the amounts of the non-protein nitrogen, urea-nitrogen, uric acid, creatinin, sugar and cholesterol. They also determine its carbon-dioxide content. They found that the carbon-dioxide content and the non-protein nitrogenous constituents may be normal. Some of the cases showed only diminished carbon-dioxide content. Others showed a normal carbon-dioxide content, but a marked retention of the non-protein nitrogen constituents, and finally some cases showed both a diminished carbon-dioxide content and a retention of the non-protein nitrogen fractions. This would indicate that acidosis based on a lowered carbon-dioxide content of the blood is not a constant or uniform finding. The sugar and cholesterol content of the blood are either normal or high, and not related to either the non-protein nitrogen or the carbon-dioxide content. In spite of all these variations in the chemical composition of the blood, there was no difference in the clinical picture or in the history of their cases.

Mellanby¹⁰ believes that *B-imidazolylethylamin*, which can be derived from the amino-acid histidin, is responsible for the toxic symptoms in severe diarrhea. When administered to animals this substance causes diarrhea and vomiting, respiratory depression, coma and death. Marriott³ calls attention to the fact that there is no desiccation or increase in the protein content of the blood in these animals—a condition quite different from that found in infants with toxic symptoms following diarrhea.

Schloss¹¹ also found a histamin-like substance in the blood of infants with acute intestinal intoxication.

Kahn¹² suggests that there may be some protein derivation products or certain amino-acids present in the blood which are very toxic in small amounts.

Boyd¹³ injected into animals extracts of the intestinal mucous membrane obtained from infants suffering from acute intestinal intoxication and produced in these animals symptoms resembling the severe toxic condition in infants. Injection of portal blood caused marked toxic symptoms, while systemic blood was only slightly toxic. Injections of extracts of the stools proved non-toxic.

It is interesting to note that in non-nephritic conditions other than the intestinal intoxications in infancy (pneumonia, intestinal obstruction and heat stroke), in which there is a retention of non-protein nitrogen in the blood, there also is a low water reserve. Bacon, Anslow and Eppler¹⁴ have demonstrated that the rise in concentration of blood non-protein nitrogen observed in intestinal obstruction is due, not to that condition *per se*, but to the accompanying water loss, and that an increase of blood non-protein nitrogen in intestinal obstruction may be prevented by the administration of sufficient water.

The quotations from the literature already given include most

of the work which relates to the present study.* In summary, it may be said that when loss of fluid from the body occurs as a result of diarrhea and vomiting, or when insufficient fluid is taken, dehydration of the tissues takes place. In certain dehydrated infants severe toxie symptoms may develop. Studies made when toxie symptoms are present demonstrate a retention of non-protein nitrogen constituents of the blood and an acidosis. There is little kidney pathology in these cases. The explanation has been offered that both the acidosis and the retention in the blood of non-protein nitrogenous waste products are due to the same cause—functional failure of the kidney due to lack of water.

Our own studies were made on 35 patients, all of whom showed clinical evidence of dehydration. In some there were marked toxic symptoms; in others these symptoms were milder in degree, and in still others a toxic state was not in evidence. By toxic symptoms we mean those previously described in this paper. Repeated blood studies were made in only a few of the infants, because we were loath to remove blood too frequently. We determined in every case the blood urea nitrogen, and in most cases the blood uric acid, feeling that these tests gave adequate evidence of renal function from the point of view of blood chemistry. In some cases the phenolsulphonaphthalein excretion in the urine was noted. In most instances the amount of blood obtained permitted a study of the CO₂ capacity of the blood plasma. In addition, the pH of the blood plasma was determined in several cases. Sodium bicarbonate was given to only 2 of our cases. These are noted in the tables. The usual clinical examinations of the blood and urine were performed, and when an autopsy was obtained the kidneys were studied for evidence of pathology.

TABLE I.

Case No.	Urea N, mg. per 100 cc.	Uric ac., mg. per 100 cc.	CO ₂ cap., vol. per cent.	pH.	Result.	Remarks.
I . . .	38	6.8	19	..	Died in less than 24 hrs.	First test 10 days before death.
II . . .	144	6.0	16	..	Died in less than 24 hrs.	
III . . .	33	Died in less than 24 hrs.	
	21	1.8	54			
IV	7.37	Died in less than 24 hrs.	No hyperpnea.
V . . .	47	8.8	36	..	Died in less than 2 days	
VI . . .	30	..	39	..	Died in less than 2 days	
VII . . .	59	Died in less than 5 days	
VIII . . .	47	..	27	..	Recovered	
IX . . .	82	12.6	26	..	Recovered	
X . . .	17	9.2	26	..	Recovered.	

* The comprehensive paper of Marriott³ covers the subject of pathology of nutrition in infancy.

In the group of patients given in Table I there were several features in common. They were all of the intestinal intoxication type, with marked dehydration as evidenced by depressed fontanel and relaxed inelastic skin. These infants could be classified clinically as very sick and toxic. Albumin was present in the urine of every infant, and casts were found in the urine of all but 1. In all but 1 vomiting and diarrhea occurred; more than three stools in twenty-four hours. A leukocytosis greater than could be explained by blood concentration was noted frequently. Usually there was an elevation of temperature. Alteration in the respiratory rate and rhythm amounting to hyperpnea was a feature in all but 1 infant (Case VII).

Analyzing the findings in this group, it is seen that a decided retention of the non-protein nitrogen constituents in the blood was quite constant, occurring in practically all cases. In 1 infant (Case III) the urea* nitrogen was only slightly increased shortly before death, although distinctly increased ten days before that time. In another infant (Case X) the uric acid was decidedly above normal, although the urea nitrogen was practically normal. Lowering of the alkali reserve was demonstrable in all but 1 patient when the CO₂ capacity† of the plasma was examined. In an infant suffering from intestinal intoxication (Case IV) the pH‡ was normal. Unfortunately, from this infant there was not enough blood available for other tests.

The blood was examined also in a case of severe intestinal intoxication occurring in a boy, aged seven years, who was moderately dehydrated, had slight hyperpnea and high fever. The blood was taken about eighteen hours before death and the findings were as follows: Case XI: Urea nitrogen, 42 mg. per 100 cc; CO₂, 40 vol. per cent.

In an infant suffering from tuberculous meningitis, and somewhat dehydrated from lack of fluid but not vomiting or having diarrhea, the findings in the blood taken ten hours before death were as follows: Case XII: Urea nitrogen, 15 mg. per 100 cc; uric acid, 3.6 mg. per 100 cc; CO₂, 63 vol. per cent; pH of plasma, 7.36.

In another infant presenting the symptoms of intestinal intoxication, but found on examination and autopsy to have had acute miliary tuberculosis, the findings were as follows: Case XIII:

* Schloss,⁹ using the urease method of Van Slyke and Cullen, found the blood-urea nitrogen in normal infants to be from 4.9 to 14.6 mg. per 100 cc. The figures given for older children are seldom above the upper limit given by Schloss when the factor of food is eliminated. All our patients were infants. The blood was taken in the morning after the second feeding of the day, the food in all cases was a modification of milk. The normal uric acid in the blood in infancy is between 1 and 4 mg. per 100 cc.^{15 16}

† The CO₂ capacity of normal blood plasma varies from 55 to 75 volumes per cent per 100 cc.^{12 16}

‡ The pH was done by the method of Cullen by which the normal limits are 7.3 to 7.5.

Urea nitrogen, 15 mg. per 100 cc; uric acid, 2.5 mg. per 100 cc; CO₂, 57 vol. per cent.

The findings in Case III and the last 2 cases just cited (XII and XIII) would indicate that increased non-protein nitrogen constituents in the blood and a lowered CO₂ capacity of the blood plasma are not necessarily present as terminal phenomena.

TABLE II.

Case No.	Urea N, mg. per 100 cc.	Uric ac., mg. per 100 cc.	CO ₂ cap., vol. per cent.	Result.	Remarks.
XIV . .	25	2.44	35	Died in 5 days	Soda, 50 gr., in the 24 hrs. before death.
XV . .	28	Died in 5 days	
XVI . .	23	3.50	25	Died in 5 days	
XVII . .	14	3.60	52	Died in 6 days	
XVIII . .	26	...	45	Recovered	pH of plasma 7.43.
XIX . .	45	5.60	53	Recovered	
XX . .	16	Recovered	
XXI . .	12	3.70	39	Recovered	
XXII . .	30	Recovered	
XXIII . .	22	...	54	Recovered	
XXIV . .	12	3.60	49	Recovered	
XXV . .	27	...	53	Recovered	

In Table II are shown a group of infants with intestinal intoxication who, while distinctly dehydrated, were not so sick or toxic as those of the group shown in Table I. In this group there was no clinical evidence of hyperpnea. Diarrhea was usually present and vomiting occurred in most infants, but these symptoms were milder in character than in the first group. Albumin was always found in the urine, while casts were present in all but 4 instances. Slight fever and mild leukocytosis were the rule.

In analyzing the findings in the infants noted in this table it is found that while the non-protein nitrogen retention in the blood, as demonstrated by urea-nitrogen determinations, was present in all but 4 infants it was less than in the more toxic patients of the first group. There was a decided lowering of the CO₂ capacity of the plasma in only 2 infants, 3 other infants showing a slight lowering of the CO₂ capacity. The 33 per cent mortality of this group contrasts sharply with the 70 per cent mortality of the more toxic group.

The patients whose examinations are noted in Table III had clinical evidence of dehydration, but were not toxic nor hyperpneic at the time that their blood was examined. None of these infants vomited, and only 2 (XXVII and XXXII) had diarrhea. A trace of albumin was found in the urine of all but 1 infant, but casts were present in only 4 of the specimens examined. There was an ele-

vation of temperature in 2 infants (Cases XXVIII and XXXII). All these cases were diagnosed malnutrition (athrepsia), except in Case XXVII where dehydration was probably due to a pyelitis, in Case XXXII which was one of convalescent intestinal intoxication and in Case XXXV where dehydration was dependent upon pyloric stenosis. This last infant did not present vomiting as a feature at the time of examination because of the frequent gastric lavage.

TABLE III.

Case No.	Urea N, mg. per 100 cc.	Uric ac., mg. per 100 cc.	CO ₂ cap., vol. per cent.	pH.	Result.	Remarks.
XXVI . .	12	1.7	Died in 20 days	
XXVII . .	17	2.1	66	..	Recovered	Sod. bicarb., 60 gr., each day for 4 days before test; pyelitis.
XXVIII . .	11	1.0	59	..	Recovered	
XXIX . .	22	2.1	48	..	Recovered	
XXX . .	19	4.8	..	7.37	Recovered	
XXXI . .	15	4.8	68	7.39	Recovered	Exam., July 16, 1923.
	15	4.0	69	7.39	Exam., July 18, 1923.
	12	3.4	53	Exam., July 31, 1923.
XXXII . .	10	3.2	67	7.47	Recovered	Convalescent intestinal intoxication.
XXXIII . .	10	Recovered	
XXXIV . .	19	Recovered	
XXXV . .	12	2.1	Recovered	Pyloric stenosis; oper- ation later.

An analysis of Table III shows that, although a few infants had an increase in the non-protein nitrogen of their blood, the rise was slight. In no infant was a definite acidosis demonstrated by lowered CO₂ capacity of the plasma nor by a change in the reaction of the plasma as determined by its pH. Recovery occurred in all but 1 infant.

From various studies (9, 17, 18, 19, 20) it has been found that the phthalein elimination in normal infants is about the same as in normal adults. Tileston and Comfort¹⁸ state that the phthalein test probably shows better than any other one method the degree of impairment of renal function. In the diagnosis of uremia it is inferior to blood analysis, for a low phthalein output may occur without retention of nitrogen. Schloss¹¹ notes that the interpretation of the lowered phthalein output in terms of renal permeability cannot be made, owing to the greatly diminished secretion of urine. In the series of patients on whom the test has been done by us the degree of diminution of phthalein elimination in the urine has coincided fairly well with the severity of the toxic

symptoms. The number of infants, however, is too small to justify conclusions.

TABLE IV.—PHENOLSULPHONEPHTHALEIN TEST (PHTHALEIN ESTIMATED ON CATHETERIZED SPECIMEN AT END OF TWO HOURS.)
(DUNNING COLORIMETER).

Case No.	Urine, amount in 24 hrs., cc.	Phthalein, per cent, 24 hrs.	Albumin.	Casts.	Urea N, mg. per 100 cc.	Uric ac., mg. per 100 cc.	CO ₂ cap., vol. per cent.	Dehydration.	Diagnosis.	Result.
XV.	..	10	28	++	Int. intox.	Died.
XXV.	98	10	+	+	27	..	53	++	Int. intox.	Recovered.
XIX.	..	15	+	0	45	5.6	53	+	Int. intox.	Recovered.
XXXV.	74	15	++	0	12	2.1	..	++	Pylo. sten.	Recovered.
VIII.	..	30	++	+	47	..	27	++	Int. intox.	Recovered.
XVI.	..	40	+	+	23	3.5	25	++	Int. intox.	Died.
XXVI.	210	40	++	+++	12	1.7	..	+	Athrepsia	Died.
XXVIII.	308	50	+	0	11	1.0	59	+	Athrepsia	Recovered.

* Hyaline.

† Granular.

TABLE V.—HYDROGEN-ION CONCENTRATION OF BLOOD PLASMA.

Case No.	pH.	CO ₂ cap., vol. per cent.	Urea N, mg. per 100 cc.	Uric ac., mg. per 100 cc.	Dehydration.	Toxic.	Diagnosis.	Result.	Remarks.
XXX.	7.37	..	19	4.8	++	0	Athrepsia	Recovered	Moribund.
XII.	7.36	63	15	3.6	+	..	Tb. men.	Died	
XXXI.	7.39	68	15	4.8	++	0	Athrepsia	Recovered	
XXXII.	7.36	69	15	4.0	+	Convalescent.
XXXII.	7.47	67	10	3.2	++	0	Int. intox.	Recovered	
XXIII.	7.43	54	22	..	+	+	Int. intox.	Recovered	
IV.	7.37	+	++	Int. intox.	Died	

Table V shows 6 of our patients in whom the acid-base equilibrium was determined by examination of the pH and CO₂ capacity of the plasma. In 3 of the infants (Cases XXX, XXXI, XXXII) there were no toxic symptoms, although definite dehydration was present. Case XII was that of an infant with tuberculous meningitis who was moribund at the time of examination. Case XXIII was an infant convalescing from intestinal intoxication who was still having diarrhea and who was somewhat sick and restless. The blood-urea nitrogen in this infant was slightly elevated. We were

not surprised to find a normal acid-base equilibrium in these 5 infants. Case IV, however, was that of an infant with typical intestinal intoxication, who died in less than twenty-four hours after having several convulsive seizures. The temperature was 106.4° F. at the time of removal of blood. It was unfortunate that from this infant sufficient blood was not available to do the other tests.

TABLE VI.

Case No.	Urea N, mg. per 100 cc.	Uric ac., mg. per 100 cc.	CO ₂ cap. vol. per cent.	pH.	Dehydration.	Toxic.	Albumin.	Casts.	Hyperpnœa.	Diagnosis.	Kidney.
XIV	25	2.4	35	..	++	+	+	0	0	Int. intox.	Very slight cloudy swelling of tubules; no true nephritis.
I	Blood tested 10 days before death	38	6.8	19	..	+++	+++	+++	++*	Int. intox.	Slight cloudy swelling of tubules; no true nephritis.
IV	Blood tested day before death	7.37	..	++	++	++	0	Int. intox.	Slight cloudy swelling of kidney with some congestion; no true nephritis.
XI	42	..	42	..	+	++	+	++*	++	Int. intox.	Low-grade cloudy swelling; no true nephritis.
XVII	Blood tested day before death	14	3.6	52	..	+	+	+	0	Int. intox. (mild)	Cloudy swelling; mild glomerular change due to epithelial degeneration; no true nephritis.
XII	15	3.6	63	..	+	+	+	0	+	Tb. meningitis	Granular degeneration of tubules and slight cloudy swelling; no true nephritis.
A.	Blood tested day before death	+++	+++	+	++*	Int. intox.	Granularity and flattening of epithelium; glomeruli loose and vacuolated; connective tissue increased; atrophy of tubules; subacute non-suppurative nephritis of low grade.
B.	+++	+	+	0	0	Premature, bronchopneumonia	Congestion; low-grade degeneration of epithelium; a few glomeruli much compressed; thin coagulum in capsular space.
C.	++	+	+	0	0	Cong. adhesion at pylorus	Much congestion; cloudy swelling of epithelium; interstitial cells numerous; low-grade non-suppurative interstitial infiltration.
D.	+	+	0	0	+	Pyloric stenosis	Moderate congestion; low-grade cloudy swelling; no true nephritis.

* Hyaline.

† Granular.

To state this pathological study of 10 cases briefly: The kidneys from 4 cases of intestinal intoxication did not show true nephritis, even though in 3 of these cases both the retention of non-protein nitrogen constituents and lowered CO₂ capacity of the plasma had been demonstrated. The changes in the kidneys usually consisted only of cloudy swelling. A fifth case of intestinal intoxication in which blood studies had not been made showed a low-grade interstitial nephritis. Of 2 cases dehydrated and toxic because of pyloric stenosis, 1 showed only slight swelling of the kidney and the other showed a low-grade interstitial infiltration. In a case of prematur-

ity with dehydration there was congestion and granular degeneration of the kidney, the terminal bronchopneumonia perhaps complicating the interpretation of the pathological findings. In the discussion of these results we can do no better than repeat the comments of Schloss:¹¹ "It seems apparent that the impairment of renal function in intestinal intoxication cannot be due in the majority of cases to a definite kidney lesion, but must depend upon some other cause. It seems most probable that the cause lies in the depleted water supply of the body."

The clinical examination of the urine in the cases in our series revealed little of value. Albumin was present in all but 1 case; sugar was found in 2 of the severe intestinal intoxication cases; traces of acetone were quite common and casts were the rule. In the 10 severely sick patients with intestinal intoxication casts were always present; in the 12 milder cases of intestinal intoxication casts were absent in 4 instances; in the 10 dehydrated cases without toxic symptoms casts were absent six times. The toxic cases, however, usually had fever, and casts are such a common finding in the urine in any febrile disturbance in infancy that their appearance probably has little significance.

Conclusions. In infants who had clinical evidence of dehydration the determination of the blood-urea nitrogen, uric acid and the carbon-dioxide capacity of the blood plasma showed different values, depending upon whether or not the infants were suffering from toxic symptoms and hyperpnea.

If no toxic symptoms were observed the blood non-protein nitrogen constituents were practically normal. If moderate toxic symptoms were present there usually was a moderate increase of non-protein nitrogen constituents, but if the patient showed distinct evidence of toxic symptoms the blood-urea nitrogen and uric acid usually were decidedly increased over normal, but the increase was neither consistent enough nor great enough to indicate that uremia was a primary cause of the fatal termination.

A decrease in the carbon-dioxide capacity of the blood plasma was found when the dehydrated infants showed clinical evidence of hyperpnea. In other infants in whom hyperpnea was not noticeable, but who were moderately toxic and whose blood usually contained an increase in non-protein nitrogen constituents the plasma showed a diminished carbon-dioxide capacity in some instances. Usually, however, the carbon-dioxide capacity of the plasma was normal when there was no increase in the respiratory rate and depth.

The pH of the blood plasma was normal in 5 dehydrated infants who did not show a decrease in the carbon-dioxide capacity of the blood plasma. In 1 severely toxic infant with hyperpnea the pH was within normal limits.

The results of the study of the pH and the carbon dioxide of the plasma would indicate that the acid-base balance was usually

greatly diminished before death. However, since in several infants this did not occur, and since in several with equally low acid-base balance recovery followed, it would seem that the acidosis is an accompanying phenomenon and not a primary cause of either the condition or its fatal termination.

The phenolsulphonephthalein elimination by the kidney corresponded to the severity of the toxic symptoms.

Histological examination of the kidneys of 10 infants who came to autopsy showed little evidence of pathology. This would furnish additional proof that the retention of blood-urea nitrogen and uric acid was not due to nephritis, but apparently to dehydration *per se*.

We wish to express our deep appreciation to Dr. Glenn E. Cullen and Dr. Herbert Fox for their coöperation in this problem.

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A CASE OF ACUTE POSTHEMIPLEGIC CHOREIFORM MOVEMENTS ON THE UNPARALYZED SIDE; STUDY OF THE BASAL GANGLIA.*

BY JAMES HENDRIE LLOYD, M.D.,

AND

N. W. WINKELMAN, M.D.,

PHILADELPHIA.

(From the Neurological service and the Laboratory of Neuropathology of the Philadelphia General Hospital.)

THE pathology of the basal ganglia, especially the striate body, which is now attracting so much attention, is not often illustrated

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by very acute cases, if we exclude the cases of lethargic encephalitis. Parkinson's disease and Huntington's chorea are usually chronic affections and long years may elapse before the lesions come to be studied. Moreover, it is by no means determined as yet what the true pathology of these and kindred affections is; but the tendency is to seek for the lesions in various parts of the corpus striatum. In view of these facts a very acute case of violent choreiform movements, coming on suddenly in an old case of hemiplegia, confined entirely to the unparalyzed side and coming to autopsy in a few weeks after the onset, is one of especial interest and has been thought to merit a report, along with a description of the lesions.

The patient, a white man, aged fifty-nine years, had had a stroke of paralysis of the right side with slight aphasia three years before. The aphasia had gone and the man was walking with a cane. He one day began suddenly to have choreiform movements which were confined to the left or unparalyzed side. These movements were violent and not unlike those seen in Huntington's chorea. His head and left arm and leg (especially the arm) were in constant motion. The head was jerked about, and the arm and leg thrown out in wide irregular movements. These movements were greatly increased when the patient was spoken to, at which time he had explosive laughter or weeping, as seen in pseudobulbar palsy. His speech was indistinct, but he had no trouble in chewing and swallowing. His mind was clear. His personal and family history were unimportant. There had been no venereal infection, but there was a good deal of arteriosclerosis. The tests for syphilis were negative. He was admitted to the Philadelphia General Hospital, and his case carefully noted from day to day. The movements were continuous except during sleep. A bedside note taken ten days after his admission was to the effect that the movements were not growing less, and the patient seemed to be more unstable, crying and laughing automatically at times and jerking his head from side to side; his whole left side being in constant choreiform movement. He was becoming slightly delirious and some rales were heard in his chest. He now developed a bronchopneumonia, from which he died a few days later; about three weeks after the sudden appearance of the choreiform movements.

Pathology by Dr. Winkelman. Grossly, aside from an arteriosclerosis, the brain showed but little. Serial sections in celloidin were made in the frontal plane and stained with Weigert's myelin sheath stain, toluidin blue and hematoxylin eosin.

On the left was a large area of old thrombotic softening which involved the greater part of the caudate nucleus, putamen, globus pallidus and the knee of the internal capsule, with secondary pyramidal tract degeneration, explaining the old hemiplegia on the right side of the body, with aphasia. (Fig. 1.)

On the right as explanation for the choreiform movements was an area of softening, more recent and smaller. It involved a narrow strip along the inner margin of the putamen, but extended into the outer portion of the globus pallidus, as seen particularly in Fig. 4. The internal capsule was involved to a very small degree in its posterior portion by a hemorrhage which impinged on the Corpus Luysi and extended into the pes pedunculi. (Fig. 5, 1a). This hemorrhage was *not* agonal.

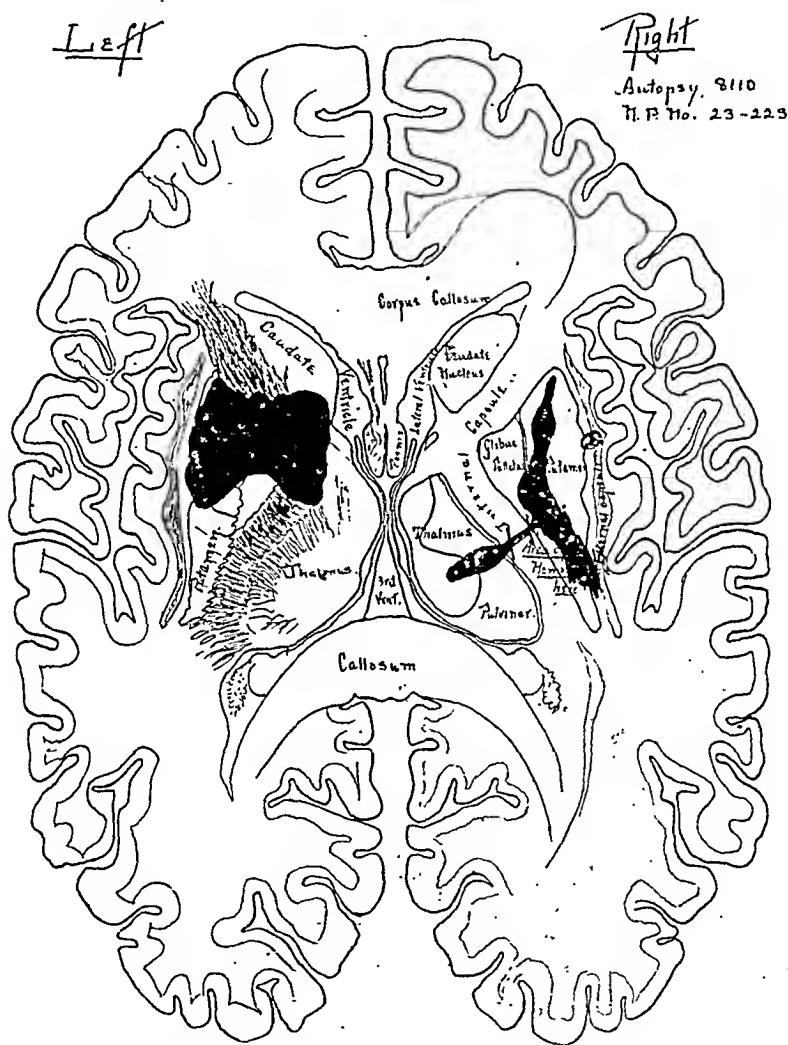


FIG. 1.—Diagrammatic representation of extent of lesions as would be seen on transverse section, reconstructed from frontal sections. The areas of softening shown in black.

Arteriosclerosis was marked; and even the smallest vessels stood out. Around some of these vessels were small areas of softening as seen in Fig. 3. A general medullary fiber poverty could be noted in the striatum, particularly on the right, with a generalized atrophy. (Fig. 4). The red nuclei and substantia nigra were normal. The

thalami on both sides were involved by gross, though small areas of softening and hemorrhage. (Fig. 5).

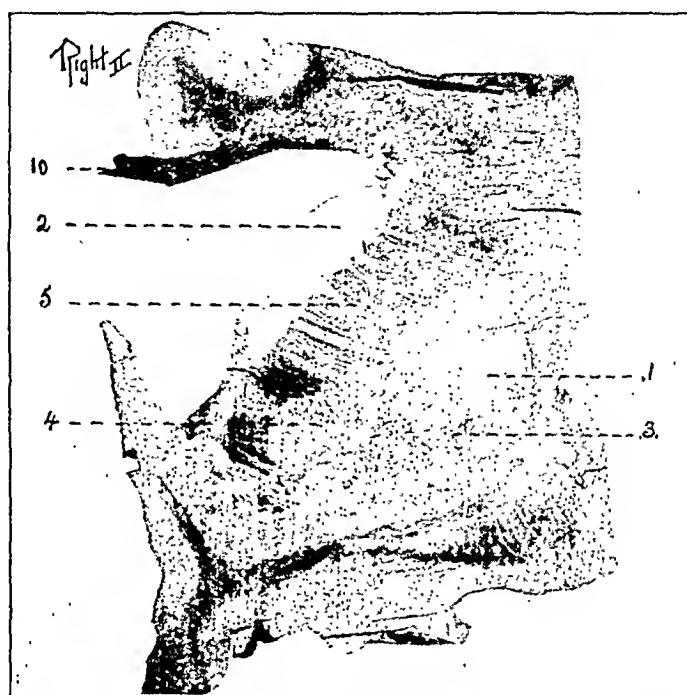


FIG. 2.—Right side. The pallidum is visible. The area of softening (at 1) is larger. Medullated fiber loss throughout pallidum and striatum.

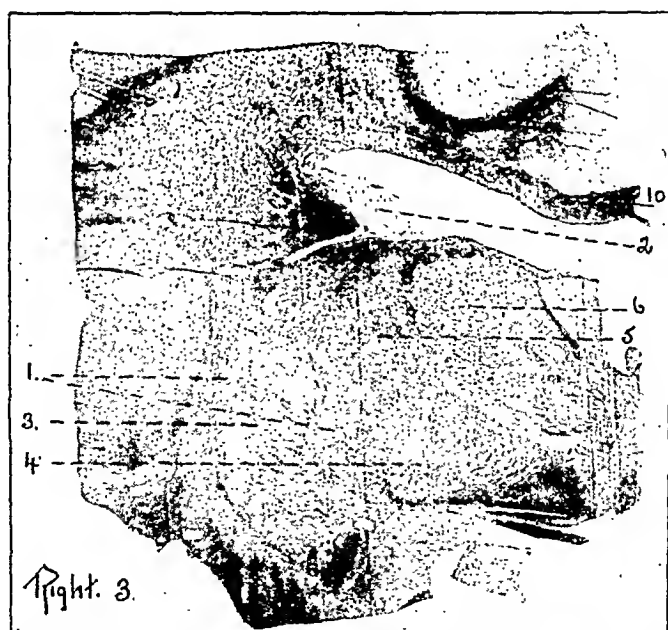


FIG. 3.—Multiple areas of focal softenings in pallidum and striatum. Ansa lenticularis small.

Toluidin blue sections showed a normal number of cells in both striatum and pallidum, except in the small foci demonstrated by

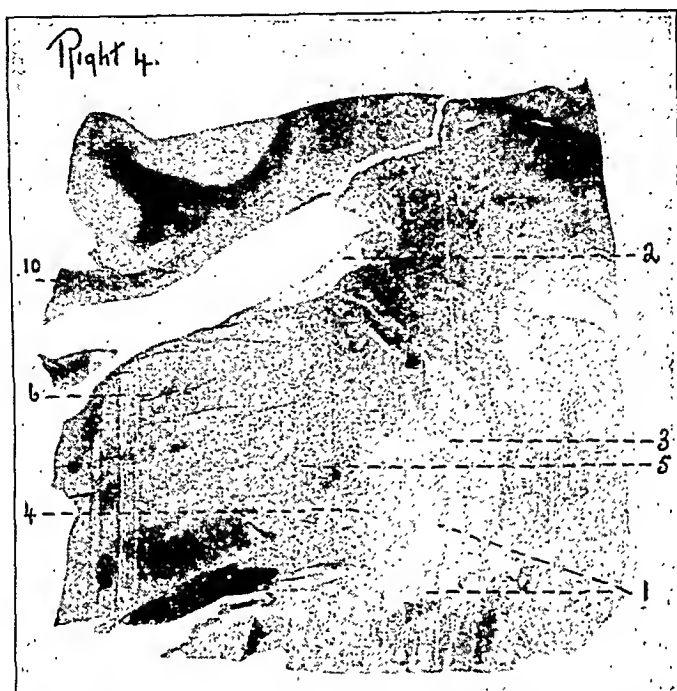


FIG. 4.—Area of softening at this level involves the lower part of the putamen and invades the pallidum. Ansa lenticularis degenerated. Pallor of caudate marked.

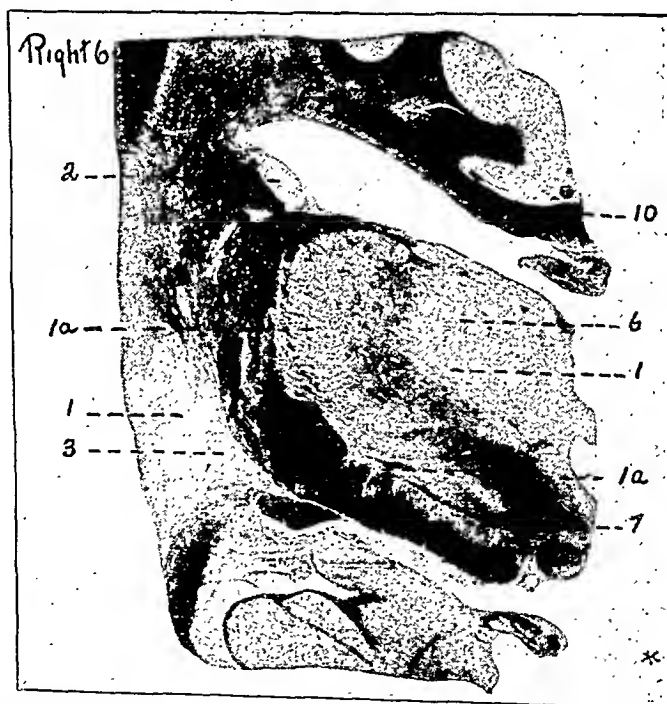


FIG. 5.—Two areas of hemorrhages (at 1a) in lateral nucleus of thalamus and in pyramidal tract in pes pedunculi impinging on corpus Luysi.

myelin sheath stains. The cells themselves showed no more pathology than is usually seen in a man of fifty-nine.

Comment by Dr. Lloyd. It is thus seen that, to use the terms which have recently been introduced, this lesion is located largely in the neo-striatum, that is, the putamen, rather than in the paleo-striatum, by which is meant the globus pallidus. It thus tends to confirm the view of some recent observers that choreic movements are caused by lesions of the neo-striatum, whereas the Parkinsonian syndrome is due to a lesion of the pallidum. What reliance is to be placed on this distinction, I do not pretend to know. The paleo-striatum, according to this view, is older, represents lower brain centers, and is not directly connected with the brain cortex. It is a rudimentary

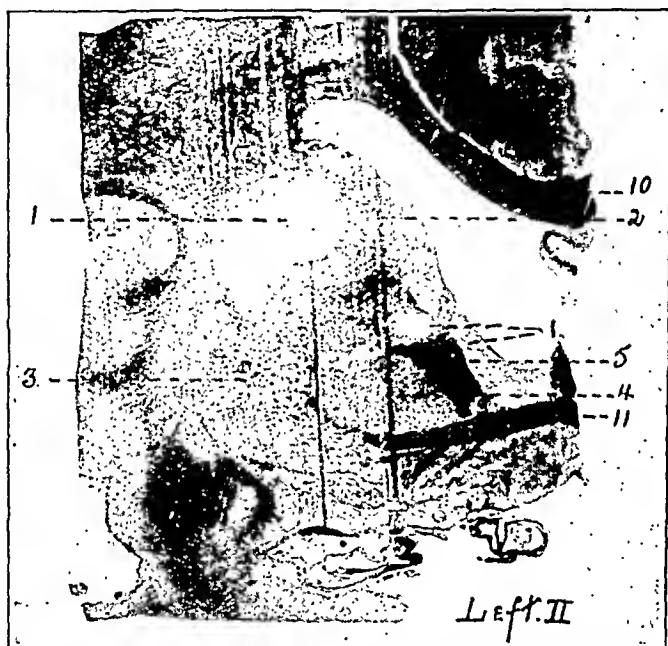


FIG. 6.—Left side. Many areas of softening, large and small, accounting for a right hemiplegia of three years' duration.

or vestigial organ, and its pathology needs to be investigated with great care. If it is simply a vestige, handed down from a remote ancestry in the prevertebrates, it may have little or no normal function left: but this would not prove that it might not have an injurious influence on normal or contiguous structures when it becomes diseased. It is significant that practically all we know about any part of the corpus striatum is derived from a study of its pathology. Its normal functions are entirely unknown, or the subject of mere guess-work. Its newer part, the neo-striatum, composed of the putamen and caudate nucleus, is only newer in a very remote phylogenetic sense, and it falls into the same category with the pallidum when it comes to interpreting its pathology.¹

¹ A preliminary note on the Morphology of the Corpus Striatum and the Origin of the Neo-pallidum by G. Elliott Smith, *Jour. of Anat.*, 3, (1919) 271.

At a meeting of the Paris Neurological Society, in 1921, Souques¹ claimed that the various clinical syndromes are related to the corpus striatum as follows:

1. Destructive lesions of the paleo-striatum, or pallidum, cause the Parkinsonian syndrome.

2. Destructive lesions of the neo-striatum, or putamen, cause either Huntington's chorea or double athetosis.

3. Lesions of the paleo-striatum and neo-striatum cause Wilson's disease, or the pseudosclerosis of Westphal and Strumpell.

Some of these lesions are also associated with changes in the red nucleus and locus niger. Into all the speculation to which this obscure subject leads I have not time or inclination to enter. The Vogts² have written an elaborate paper on diseases of the striate system. They refer to a case of Liepmann of a woman who developed choreic movements in the right arm and leg and later had a hemiplegia of the opposite side—hence not unlike the present case. At autopsy there was found degeneration of the left caudate nucleus, the anterior part of the internal capsule and the oral half of the putamen, almost the same as in our case.

I suggest that it is at least possible that all these syndromes may be caused by lesions in a vestigial organ acting in various ways on the motor paths in the internal capsule.

KEY TO FOLLOWING FIGURES.

(All frontal sections.)

- | | |
|-------------------------|-------------------------------------|
| 1. Area of softening. | 7. Peduncle. |
| 1a. Area of hemorrhage. | 8. Red nucleus. |
| 2. Caudate nucleus. | 9. Substantia Nigra. |
| 3. Putamen. | 10. Corpus callosum. |
| 4. Globus Pallidus. | 11. Anterior commissure. |
| 5. Internal capsule. | 12. Pyramidal tract degeneration in |
| 6. Thalamus. | peduncle. |

N.B.—In a few cases the sections have been reversed in the printing. This is denoted by a star in the right lower corner.

SYPHILIS OF THE DIGESTIVE ORGANS.*

BY WESLEY E. GATEWOOD, A.M., M.D.,

IOWA CITY, IOWA.

(From the Medical Department, State University of Iowa, Iowa City, Iowa.)

THE symptoms and signs presented by syphilis of the liver and syphilis of the stomach, and to a less extent by syphilis of the

¹ Rev. Neurol., 1921, 37, 534.

² Jour. f. psychol. u. Neurol. 1920, 25, 828.

* Read before the annual assembly of the Tri-State Medical Association, Des Moines, Iowa, October 29, 1923.

pancreas, small intestine and colon, have gradually become definite clinical entities, sufficiently well studied that antemortem diagnosis of these diseases may be made with considerable accuracy. In a review of our series of 12,000 admissions into the medical department of the University Hospital we find that among a large number of syphilitics there were only a few (0.37 per cent) with syphilitic disease of the digestive organs. The liver, probably because of its size, its immense blood supply and function of detoxication, more frequently is sufficiently diseased to produce recognizable clinical symptoms and signs.

Syphilis of the Liver. In a careful study of our records we find that syphilis produced clinical evidence of changes in the liver of 21 individuals. In only 1 instance among 470 secondary syphilitics was there any sign or symptom indicating syphilitic damage in the liver. In this 1 patient there was a history of slight but definite jaundice early in the secondary eruption but jaundice was not observed by us in any of these 470 patients, nor was the liver pathologically enlarged. Jaundice occurring early in syphilis, during the so-called secondary stage, may occur in two forms, the mild icterus which is symptomatically like ordinary acute catarrhal jaundice and usually runs a somewhat similar course, and the severe jaundice (icterus gravis) which is still much more uncommon and presents clinically the features of acute yellow atrophy. Both of these types are well described by Wilc¹ in a review of his own cases and those which he collected from the literature. The incidence of the mild form at the University Hospital of Michigan was only 3 in 500 cases of secondary syphilis. The mild icterus may probably be considered as an acute visceral exanthema with edematous and catarrhal changes within the organ. The severe form may rarely follow the mild form if this be prolonged. It is more properly a severe parenchymatous hepatitis due to the toxins of the spirochete. The literature of acute yellow atrophy of the liver and icterus gravis syphilitica states that about 10 per cent of acute yellow atrophy is due to syphilis. This form of syphilitic disease of the liver has not been discovered in this Clinic.

In the tertiary or late stage of the disease we may consider three clinical forms of liver change, namely, the gummatous or circumscribed, the cirrhotic or diffuse type with combinations of these 2 types, and third, amyloid liver occurring as a part of a general amyloidosis in tertiary syphilis. The diffuse or cirrhotic type is by far the most common. Amyloid disease of the liver is the least common change in the liver due to syphilis and the most difficult to diagnose. The gummata may vary enormously in size as noted particularly in 1 of our cases.

A white woman, aged twenty-one years, two and a half years after a primary genital sore, had noted a tumor mass in the epigastrium which at times must have been 6 inches or more in diam-

eter. The mass would enlarge rapidly in three or four days and become very hard, gradually decrease in size in the next three or four weeks and soften. According to our belief it was smaller at the time when she was admitted and the mass was then about the size of an orange and located in the left epigastrium, originating in the left lobe of the liver. It actually melted away when large doses, up to 130 gr. a day, of potassium iodid were given. The dull aching pain and the liver enlargement had existed for nearly fourteen months. She had lost about 44 pounds. There was a very slight fever, at times up to 100° F. The spleen was markedly enlarged. The serum Wassermann was four plus.

The diffuse involvement causes either an enlarged or a small liver, depending chiefly upon the stage when the disease is recognized. Early the changes may closely resemble those encountered in the hypertrophic or biliary cirrhosis. Late in the disease the organ becomes shrunken, both clinically and pathologically resembling the atrophic or Laënnec's form of cirrhosis. There has been much discussion as to the relation between syphilis and alcohol in the production of the small hard and nodular cirrhosis, particularly as both etiological factors are often present in the same individual. Owen² in reviewing the literature and reporting his own series of cases stated that the present evidence indicates that very commonly syphilis or a combination of syphilis and alcohol are etiological in producing the nodular cirrhosis.

Among 167 cases of tertiary syphilis not including involvement of the central nervous system syphilitic disease was diagnosed twenty times. Of these, 10 were chiefly of the cirrhotic type, in 7 the changes were chiefly gumma formation, and in 3 there were well-marked cirrhoses as well as palpable gummata. Clinically syphilis of the liver is much less commonly recognized than are definite changes found at postmortem. This is readily explained in that the less severe changes often fail to produce any sign or symptom and that a large proportion of the livers have only capsular scars as their chief gross evidence of syphilis when examined at autopsy.

Of the 20 cases there were 12 males and 8 females. The average age of the patient was forty-three years; the youngest was a woman of twenty-one years and the oldest a man of seventy-one years. Four were thirty or younger. There were no congenital cases. In 9 of the individuals the occurrence of the primary sore was either denied or the date of its occurrence unknown. The average time elapsed after the primary sore in those cases where a primary was admitted was ten and a half years. The longest time elapsed was forty-one years and the shortest was one and a half years. In none of the cases had there been any early antisyphilitic treatment. The use of alcohol was admitted in 7 of the cases, by 3 to excess, by 3 moderately and by 1, a little.

The duration of symptoms referable to liver disease was from two weeks up to eight years. The symptom of pain or distress was quite variable. In 7 there was no distress of any sort. In 5 there had been dull but not severe pain in the region of the liver, in 3 moderately severe pain and in 5 agonizing pains similar to those occurring in attacks of gall stones (Portis³). Those in which there was a dull distress or moderate pain usually described this as located in the pit of the stomach or under the right costal margin, but at times the pain was under the left costal margin. It was often mentioned in our histories as a dull dragging sensation or feeling of fulness and heaviness, in some cases increased at once by eating, in others not at all influenced by food. In several the pain was worse at night. In those who had severe attacks of pain the pain was described as originating under the right costal margin, radiating up into the chest in some cases and increased by deep breathing, in others referred to the right scapular region or directly through or around to the right back. In some cases there were several such acute attacks with more or less continuous distress between the attacks.

A tumor mass or enlargement in the upper abdomen was felt by the patient in five instances.

Vomiting was one of the chief symptoms in 1 case and was present in 2 others. The appetite was described as good in 14, fair in 3 and poor in 3. The weight loss varied from slight up to 50 pounds and where the amount was definitely known it averaged 20 pounds. One patient gained 14 pounds above his usual weight; this gain was largely due to edema and ascites.

In 5 of the patients there was history of fever accompanying the illness and in 3 of these also a history of chills. Two had rigors during their hospital stay. In 9 cases the temperature charts showed some fever and in 3 this exceeded 101° F. (Rolleston,⁴ Friedman³).

Jaundice was recorded in 8 cases and in 3 was quite marked and prolonged. In 2 the stools were clay-colored and 6 had bile in the urine.

Hematemesis and melena occurred on several occasions in 2 cases. In 5 there was ascites, in 2 slight, in 1 moderate and in 2 marked ascites. The amount removed from one totaled 17,450 cc of which 7750 cc were removed at one tapping. In 1 patient there was a well-marked caput medusæ.

The liver was enlarged markedly in 8, moderately in 8, slightly in 2, not at all in 1, and of less than normal size in 1 case. It was tender in 13 cases, as a rule only slightly. The consistency was firmer than normal and at times hard.

The spleen was definitely enlarged in 13 of the 20 patients. In 8 the spleen extended two fingers breadth or more below the left costal margin and in 1 nearly a hand's breadth below the costal margin and across to the navel.

In those cases in which gastric analyses were done there was no constant finding. In 2 there was a relatively high acidity and in the others normal down to anacidity. No gastric retention occurred in any of them.

In 13 there were other signs of syphilis such as aortitis, periosteal or bone syphilis, syphilis of the central nervous system, or scars on the genitals and elsewhere of an unmistakable character. The Wassermann was strongly positive in 15 and negative in 3 cases. In 1 the reaction had previously been positive but by treatment had been rendered negative. In 1 it was not recorded. In those cases in which there was a negative reaction syphilis was admitted and there were additional evidences of syphilis elsewhere. In 2 patients reexamined five years after the diagnosis of syphilis of the liver the blood Wassermann which at first was four plus became negative under treatment. The liver changes were not permanently improved.

All of the 7 clinical types described by Rolleston⁴ except definite amyloid disease were present in our series. There were 3 cases in which the picture resembled Banti's disease with a rather marked anemia, the spleen much enlarged and the liver relatively small. In 4 cases the picture was rather that of hepatic tumors, large gummatous masses in the liver being palpable. One case with chills and fever and a large tender liver mass which varied greatly in size and grew rapidly resembled a liver abscess. There were 5 patients in whom the symptoms and signs resembled atrophic cirrhosis with enlarged spleen, dilated collateral portal circulation, and in 1 case a caput medusæ. The remaining 7 more closely simulated the hypertrophic form of cirrhosis. We have already mentioned those cases in which the pain and the gastric symptoms resembled gall-bladder and gall-stone disease.

Obviously there are cases in which the differential diagnosis is difficult. The therapeutic test, especially the use of large doses of potassium iodid increasing to the tolerance of the individual, we have found of especial advantage in a number of cases. Gummata unlike carcinomatous masses rapidly melt under this treatment. However, in 1 of our cases the original diagnosis was carcinoma of the liver. The abdomen was explored at one of the best clinics. Gummata were found. Faithful therapy for five years thereafter failed to cure and finally larger gummatous masses were present at our last examination. The liver enlargement of passive congestion due to cardiac decompensation in the luetic presents another difficult point of differentiation. Usually the liver is less tender if the enlargement is due to syphilitic changes in it. In 1 of our cases both syphilitic myocardial disease with cardiac decompensation and hepatic syphilis were present. The liver was first involved enough to produce large ascites. Later the legs became swollen and the patient dyspneic.

Syphilis of the Pancreas. Clinically syphilis of the pancreas is rare. Walter Sallis,⁶ in 1913, was able to collect only 15 cases of clinical pancreatitis due to syphilis. The disease seems to be much more common in a form sufficiently mild not to produce clinical symptoms but to be recognized by the pathologist in cases of visceral syphilis, especially in association with syphilitic cirrhosis of the liver.

In our series of 12,000 cases among which were 23 cases of pancreatitis clinically diagnosed, only 2 instances of clinically syphilitic pancreatitis occurred, unless we include diabetics who showed evidences of syphilis, either by history, positive Wassermann reaction, or other clinical evidences of coexistent syphilis.

One of the patients referred to was a woman, aged thirty-six years, who gave a definite history of syphilis, the primary lesion having occurred fourteen years ago, and a history of several miscarriages. She had had no antisyphilitic treatment. Her present symptoms began four months before admission, the main complaint being pain and tenderness in the region of the stomach, gaseous distress, and cramping pains at once after meals, this distress chiefly epigastric with radiation to the region of the right scapula. The distress was always worse when lying on her back. There was much nausea and vomiting immediately after meals, though her appetite was good. She had lost 40 pounds since the onset of her trouble. Sugar was discovered in her urine three weeks before admission. While in the hospital she had a little irregular fever, once up to 101° F. without obvious cause and some tenderness in the region of the pancreas. The liver and the spleen were not enlarged and no tumor mass was palpable. The serum Wassermann was four plus. The leukocyte counts were normal. The urine constantly showed a trace of sugar. The duodenal contents showed a diminution of all of the pancreatic ferments. She was given two intravenous injections of diarsenol and the usual dosage of potassium iodid and mercurial inunctions. She returned in four months much improved, physically and symptomatically well. Sugar no longer appeared in the urine. The Wassermann test remained four plus.

The other patient, a man with a positive Wassermann and the clinical picture of taboparesis, showed a glycosuria repeatedly and had symptoms of polyuria, polydipsia and polyphagia lasting one month. Later under antiluetic and dietetic treatment the sugar tolerance became so great that sugar did not appear in the urine with a diet of 200 gm. of carbohydrate, 60 gm. of protein and 200 gm. of fat.

Among 286 diabetics only 5 had a positive Wassermann or history or other evidence of syphilis. Should we consider these 5 and the above described cases all as due to syphilitic disease of the pancreas it would be evident that in our series syphilis has rarely produced clinical manifestations of pancreatic involvement. We prefer to

consider these 5 diabetics with positive Wassermann tests as individuals in whom there was pancreatic disease and syphilis, the syphilis either coexistent or causative, this point remaining unproven. It would seem that with an incidence of 167 tertiary syphilitics and 286 diabetics among the 12,000 admissions, and only 7 of those who had positive Wassermanns showing a glycosuria, that though pathologically syphilitic changes may be found frequently in the pancreas, just as in the liver, spleen and aorta, much less commonly does syphilis cause the diabetic syndrome or produce clinically recognizable disease of the pancreas.

Warthin⁷ has advanced arguments from the viewpoint of the pathologist that diabetes may be frequently caused by syphilis. From the clinical side these have been well refuted by Rosenbloom,⁸ Lemann,⁹ and by Carnot and Harvier.¹⁰

Gastric and Intestinal Syphilis. Syphilitic disease of the stomach and bowel, exclusive of the rectum, we have found exceedingly rare. In a material which furnished 286 duodenal ulcers and 197 gastric ulcers of the so-called peptic type, we have found 3 cases of syphilis of the stomach, and 1 case of syphilis of the large and the small intestine, the latter case¹¹ occurring as a late manifestation in 1 of the patients with gastric and hepatic syphilis. We can scarcely enter into a discussion of the pathology, clinical types and diagnosis of gastric syphilis. It is not only essential to prove the existence of syphilis and the presence of organic gastric disease by the usual clinical methods but also to follow for some time the clinical course. One of our cases was little improved by antiluetic therapy but the nature of the process was conclusively proven at autopsy. Another is after nearly three years symptomatically cured but has a very marked hour-glass deformity of the stomach which will probably necessitate surgery.

In our entire series there were 3 syphilitics, 2 with syphilis of the central nervous system and 1 with hepatic and nasal involvement, who had the clinical picture of gastric ulcer with the usual history, laboratory and roentgen-ray and physical signs of peptic ulcer. They all responded to dietetic and alkali therapy.

The one instance of intestinal syphilis was of the extensive ulcerative type. There were marked diarrhea, large hemorrhages from the bowel, much mucus and pus in the stools, an irregular fever up to 103° F., mild delirium, marked anemia, a well-marked leukopenia, and after four months of the intestinal symptoms the patient died and an autopsy was performed. Because of absence of any evidence of tuberculosis, negative Widal tests and blood cultures, the absence of parasites in the stools, and the general clinical picture a probable diagnosis of syphilitic enterocolitis had been made antemortem.

As yet syphilitic disease of the intestine is too rare to have produced any known clinical syndrome.

Syphilitic disease of the esophagus was diagnosed once in the medical service. Practically all patients with esophageal disease are admitted into another service. Likewise, patients with rectal syphilis have usually been admitted to general surgery.

Summary. 1. Though syphilis is a relatively common disease in the medical clinic of the University Hospital of Iowa, only 45 among 12,000 admissions were for syphilitic disease of the digestive organs.

2. Clinical evidence of hepatic involvement during the secondary stage of syphilis was quite rare, occurring in only 0.21 per cent of such cases. The clinical picture in tertiary syphilis of the liver is quite varied and 6 of the 7 types described by Rolleston were recognized among the 20 cases discussed.

3. Only two instances of syphilitic pancreatitis were diagnosed. Syphilis may be a factor in the production of the diabetic syndrome, but clinically there seems to be very little relation between the two diseases.

4. Syphilis of the small intestine is extraordinarily rare. Less than a half of 1 per cent of organic disease of the stomach and duodenum is syphilitic.

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OCULAR LESIONS COMPLICATING ULCERATIVE COLITIS.

BY BURRILL B. CROHN, M.D.,

NEW YORK.

(From the Medical Department of the Mount Sinai Hospital, New York.)

THE following cases are described with the object of pointing out an unusual complication of chronic ulcerative colitis of the nature of inflammatory ocular or para-ocular phenomena. In first seeing these cases the resemblance to clinical and experimental xerophthalmia was so striking as to be convincing. On the other hand, a search of the literature disclosed a somewhat analogous condition described for specific dysentery as seen at the Eastern War front. The exact nature of the lesion may therefore remain in doubt until

further observations on such cases lead to more decisive information and data.

CASE I.—The first case was that of a woman, aged twenty years, of American birth, who had been ill with fever and diarrhea for six weeks. About two years ago, immediately after pregnancy, she suffered from a severe diarrhea which lasted continuously for nine months. During that time she had, according to her statement, an irregular fever, frequent and often uncontrollable bowel movements; she lost 40 pounds in weight. After nine months of illness she began to improve and thereafter remained well for eleven months.

Six weeks ago she suffered a recurrence of her illness. The diarrhea has been almost continuous, consisting of 8 to 12 or more bowel movements a day composed of mucus, some admixture of blood and fecal matter. The asthenia has been marked, emaciation extreme; her previous weight was 134 pounds; she now weighs approximately 70 pounds. During this last week she has complained of being almost unable to see on account of a violent inflammation of her eyelids.

The physical examination showed extreme emaciation, general abdominal tenderness, a febrile state associated with marked debility and prostration. The blood-pressure was subnormal and a marked anemia was present. During the period of observation a sigmoidoscopic examination revealed diffuse chronic ulcerative colitis, apparently of the non-specific type. The feces were repeatedly examined with the warm stage; amebes were absent. Agglutination tests of the blood against various strains of dysentery organisms were negative.

When first seen the patient insisted upon being kept in a room from which all daylight was excluded. The photophobia was intense, the eyes being kept continually covered. The report of the ophthalmologist (Dr. Mark J. Schoenberg), which accompanied her admission to the hospital, stated that an acute diffuse conjunctivitis was present; a superficial ulcerative process of the cornea was described. The exact nature of the lesion could not be ascertained but it was remarked that the process was apparently an unusual one not falling readily into any known clinical category.

Upon admission to the hospital it was determined that in spite of the severe colitis present, the state of severe emaciation called for a more liberal dietary. The exact nature of the diet during the previous weeks could not be ascertained but was reported by the patient to have been extremely limited, consisting only of fluids, cereal gruels, vegetable soups and similar bland, non-irritating substances. A liberal diet was now prescribed, including baked potato, asparagus tips, purée of peas, custard, eggs, toasted white bread and butter, the above being a sample diet recorded for one day. Local treatment for the colitis was held in abeyance.

Almost immediately a change in the clinical course took place. The inflammatory condition of the eyes resolved within two to three days; within that time the edema of the conjunctivæ and the corneal cloudiness cleared up; photophobia immediately disappeared. This fact is all the more striking in the light of the information forwarded by the ophthalmologist. He stated that all usual therapeutic means for combating an ordinary conjunctivitis had failed. Further, smears from the purulent secretion were repeatedly negative for bacteria. Within two weeks the colitis subsided, though little in the way of local treatment to the intestine had been instituted.

In the course of the last year the patient has remained well.

The immediate clearing up of the eye condition upon change from a fluid diet restricted to but one or two food substances to a diet representing all the known nutritional substances suggested that the ophthalmic picture was in some way a nutritional deficiency phenomenon analogous if not identical with xerophthalmia.

CASE II.—A few weeks later (February, 1923), the following case was admitted to the medical wards of the hospital. The patient, a married woman, aged twenty-five years, had been ill for six weeks, complaining of abdominal pain, severe, cramp-like in character and diarrhea consisting of 10 to 15 daily movements of blood and mucus. The physical examination shows a poorly-nourished woman, very pale. She has a herpetic eruption on her lower lip; the buccal mucosa and lips show numerous slightly elevated irregular opaque plaques resembling an aphthous stomatitis. A marked secondary anemia is present, the blood count reading:

Hemoglobin, 40 per cent; erythrocytes, 2,900,000; leukocytes, 8400; polymorphonuclears, 65 per cent; lymphocytes, 31 per cent; mononuclears, 1 per cent; myelocytes, 2 per cent; platelets, 350,000. Coagulation time, four minutes. The sigmoidoscopy shows the picture of an intense ulcerative colitis. Amœbæ are absent and blood tests fail to show any agglutination against various strains of dysentery bacilli. The clinical picture is that of a non-specific ulcerative colitis.

This patient also shows evidence of a marked photophobia. She lies in the ward with her eyes covered by her hand, with her head turned away from the window. The ophthalmological examination by Dr. Cyril Barnett on February 10, 1923, was reported as follows: Fundi normal. A small area of infiltration is seen at the limbus of the right cornea (five o'clock) with an erosion of the superficial epithelium and faint ciliary injection. This probably represents a reopening of an old corneal lesion.

Before admission to the hospital she had been maintained on a diet conforming with the usually accepted idea for the dietary management of an acute colitis. It had consisted strictly of boiled cereals and cereal broths, tea, meat infusions. Soon a radical

change in her alimentation was prescribed, a rather full diet including eggs, milk, butter and the tuberous vegetables being allowed. Within three days the eyes were reported as practically normal. Coincidentally a general improvement took place. The colitis was treated by irrigations with neutral acriflavine solution (1 : 4000), the colitis symptoms rapidly subsiding. Within two weeks the sigmoidoscopic control examination showed the healing process to be far advanced. The patient was discharged, well, six weeks after admission.

In this case, as in the former, the exact nature of the ocular disturbance was not completely understood until after the disappearance of the symptoms. However, it was again noted that without the institution of local treatment, prompt recovery ensued upon change of diet and the administration of a complete dietary representing all the classes of food substances rich in vitamins.

The resemblance to the clinical picture of keratomalacia or xerophthalmia seemed rather striking. Within the last year a condition almost identical with the above clinical observation has been produced experimentally in rats by Yudkin and by Yudkin and Lambert.² By maintaining these laboratory animals, for a few weeks, on a diet deficient in fat-soluble vitamin they were able to reproduce ocular lesions similar to the above clinical observations and apparently identical with the eye disturbances which under similar experimental conditions had been produced in 1908 by Falta and Noeggerath³ and in later years by Osborne and Mendel,⁴ by McCollum, Simmonds and Parsons,⁵ and by Mori.⁶

The experimental eye disturbances in the rat have been most carefully studied and described by Yudkin and Lambert. They attribute the condition to an insufficient lachrymation which results from a degeneration and inflammatory process in the paraocular lacrimal glands. Epithelial degeneration and vacuolization of the secretory tubules may take place followed by suppuration, fibrosis and atrophy. The earliest manifestations in rats is a slight photophobia, lacrimation and reddening of the conjunctivæ. The lachrymal fluid is viscid; there is edema of the eyelids. The eye lashes fall out and the lids stick together with matted secretion. The corneal surface remains smooth. However, after a time, a cloudiness of the cornea may occur with the formation of characteristic corneal plaques. This does not necessarily imply corneal ulceration for under the plaques the epithelium may be well preserved, as is shown by testing the corneal surface with fluorescein. Ulceration may come later if the dietary deficiency be prolonged. The corneal opacity consists of keratinized epithelium beneath which the deep layers of epithelial cells are generally found intact. The whole represents a low-grade inflammatory process. In the conjunctiva, Mori has described the process as due to the formation of granules of keratophylin in the cytoplasm of the secondary layer

of these cells. The same process they say cannot take place in the cornea except at the limbus; ulceration they attribute as of secondary nature and due to bacterial contaminations.

It will be noted that the clinical phenomena occurring in the above cited cases of colitis agree, even in detail, with the experimental lesion produced in the rat by a diet deficient in vitamin A. The photophobia, swelling of the eyelids, the generalized conjunctivitis, the corneal opacity occurring at the limbus and resembling a corneal ulcer—the whole process disappearing promptly upon the administration of a general diet without the further evidence of the presence of a true ulcer of the refracting tissue of the eyeball. These common features speak for the parallelism between the clinical bedside observations and the experimental lesions as observed in laboratory animals.

In 1904 Mori described, during a famine in Japan, a like lesion affecting 1400 children between the ages of two and five years. During the World War, Bloch⁷ described 40 cases, at Copenhagen, in children who were being fed on skimmed milk. The children were saved from corneal ulceration and blindness by the administration of whole milk and butter. In the experimental lesion produced by Osborne and Mendel in 1913 the lesion was immediately cleared up by feeding cod-liver oil and butter. Wilson and Du Bois⁸ recently describe a fatal case of keratomalacia in an infant of five and a half months who was fed only with condensed milk.

The condition is commonly attributed to a deficiency of fat-soluble vitamin A, and constitutes a disease which represents one of the clearest and most concrete examples of a vitamin disturbance. The primary sources of vitamin A are to be found in nature in raw milk, animal fat, egg yolk, green leaves and in the growing parts of plants. In animal tissues it is present in great abundance in liver, heart and kidneys as well as in eggs; it is richly present in milk and, of course in butter. It is less abundant in stale milk, dried milk and in boiled or pasteurized milk (McCarrison.⁹). Green vegetables and shoots contain it in liberal degree. Fruits contain it in only in small amount, except the tomato.

It will thus be seen that the conventional and accepted diet for the treatment of acute or chronic colitis is practically devoid of these food substances which harbor this element essential to health. Neither of these patients had received as part of their dietary raw milk, butter, eggs, fruits or green vegetables, all being substances supposed to aggravate diarrheal conditions and to retard healing. And if they did receive a diet including even in part some of these articles, it is unlikely that they were fed a quantity sufficient to maintain the vitamin reserve of the body. The continuous diarrhea, with its marked intestinal hypermotility, undoubtedly furthered the deficiency process by hurrying the partially digested

food out of the body before absorption from the diseased colon could be accomplished. While the human and animal body has a fairly large storage supply of vitamin A, it is apparently exhausted within five to six weeks, a period of time similar to that necessary in the rat (four weeks) before the onset of xerophthalmic manifestations.

In these two cases of colitis no claim is made that the intestinal disease is of deficiency origin, even though the rapid clearing up of the inflammatory process seemed to follow, as of cause and effect, the administration of a general diet. It might, however, be not amiss to stop for a moment to heed the warning suggestion of McCarrison who hypothetically declares that many of our cases of intestinal disorders and inflammations are of possible deficiency origin, a dietary imbalance giving rise to the condition and bacterial invasion acting only as a secondary factor.

When one considers the duration of time over which chronic ailments extend and one remembers the often monotonous or one-tone diet prescribed, it is rather surprising that one does not more often see general evil results from protracted dietary restrictions. The class of gastric dyspepsias, psychasthenic neurotics with self-prescribed dietary limitations and particularly gastric ulcer patients, who for long periods of time, are maintained on milk, or on milk and eggs without many fruits or vegetables—these may offer a fertile ground for the clinical manifestations of deficiencies in vitamin B and C classes.

In regard to the question of differential diagnoses it is of interest to remark that the literature of the last few years contains references to a form of conjunctivitis and iritis occurring as a complication of the specific form of dysenteric colitis. In the original description of Crouzon¹⁰ (1916) he associates this conjunctivitis with a form of arthritis, both occurring in the same cases of dysentery as complications during the height of the course of the disease. Among 420 cases of dysentery studied at the war front, he observed 9 cases of "rheumatism." He remarked that a peculiar form of conjunctivitis might occur before, with or after the rheumatism; that it appeared usually about the tenth to fifteenth day and only in the most severe cases. The arthritis and conjunctivitis was observed just after the cessation of the diarrhea or often with exacerbations of the temperature.

Cosse and Delord,¹¹ ophthalmologists, studied the same series of cases reported by Crouzan and give a more intimate picture of the ocular and paraocular changes which complicate this specific type of colitis. Both eyes are usually involved at once; there is no chemosis or reddening of the bulbar conjunctiva. The palpebral conjunctiva is red, particularly the inferior lid. There is a moderate mucoid secretion, but no pus. Blepharospasm and

photophobia are absent; the iris is normal. The microbiology of the conditions is absolutely negative. In one case a peripheral keratitis with iritis was observed.

They considered the condition as one of pseudo-rheumatism occurring as a complication of the dysentery. They regarded the eye condition as of toxic, or metastatic, rather than of bacterial origin.

The clinical picture, both as regards the rheumatism and the ocular manifestations, was confirmed by Graham,¹² an English observer also at the war front. He studied 50 cases of dysenteric pseudo-rheumatism many of which were complicated by the specific form of non-bacterial conjunctivitis. He adds 7 cases of the more severe class characterized by cyclitis and iridocyclitis.

Cope¹³ regards the arthritis as directly due to the *Bacillus dysenteriae* though quoting a personal communication from Sir William Campell in which the latter states that the fluid aspirated from the joints of 18 cases was entirely sterile. All observers agree that the conjunctivitis is also a sterile process, clearing up within seven days without treatment.

As regards the ophthalmic manifestations of the two cases under discussion in this paper, are we dealing with examples of nutritional disturbances of keratomalacia or xerophthalmia? Or, does there occur in non-specific ulcerative colitis a form of metastatic conjunctivitis and keratitis analogous if not similar to the condition described as complicating specific dysentery?

The analogy of the ocular condition as we have observed it, to clinical xerophthalmia as described under conditions of famine in Europe and Asia, and its similarity if not identity to experimental keratomalacia produced in rats by diets devoid of vitamin A substances, would be strong arguments in favor of its origin in an avitaminosis. On the other hand, the fact that a pseudoarthritis and a similar conjunctivitis and keratitis has been described for other forms of dysentery might induce one to believe that both conditions are metastatic complications of infectious ulcers of the colon, of whatever origin, but probably a result of secondary infections of such ulcers with pyogenic bacteria.

Summary.—All forms of colitis have, as common characteristics, certain conditions that might tend to a vitamin deficiency, that is a prolonged course, severe diarrhea, rapid loss of weight, nutritional deficiencies, and are customarily treated by a marked restriction in the dietary menu. It would thus appear possible that all the forms of conjunctivitis and keratitis described in this disease are of the same nutritional nature, namely, that of an avitaminosis, non-bacterial in origin, clearing up promptly without local treatment and improving upon the administration of a generous and general dietary.

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RINGWORM OF THE TOES AS FOUND IN UNIVERSITY STUDENTS.

BY S. H. HULSEY,

AND

F. M. JORDAN.

(From the Laboratory of Dermatological Research, Department of Cutaneous Medicine, University of Pennsylvania.)

To the average medical man ringworm of the toes appeals little because ordinarily it is such a trifling ailment. The specialist, however, is aware first that it is far more common than is generally imagined, and second, that the affection extends often enough to other parts of the body. More exactly, the toes serve as a reservoir for fungi, just as the tonsils do for pneumococci and streptococci, and from this position the disease may be transferred elsewhere, inducing an eczematoid ringworm of the hands and axilla or the well-known tinea cruris—"jockstrap itch."

Many a physician will recognize the lesion and at once will realize the frequency of this condition when its several manifestations are pointed out. It appears, with variations, in three forms. First, the familiar cracked toe and soft corn—a macerated hyperkeratosis, between the toes (generally the fourth and fifth), with moderate surrounding inflammation. Second, as an eczema—red, oozing, and furiously itchy, extending from an interdigital position such as the above. Third, as a diffuse hyperkeratosis with blisters.

The purpose of our work was to furnish precise figures as to the frequency of the affection in a uniform class of society, and to investigate certain other phases of the disease such as: (1) The duration; (2) the association of other varieties of ringworm; (3) the

influence of residence (that is, the location of the individual's home) as an etiological factor; (4) the frequency with which the fungus could be demonstrated on direct examination and in culture.

Methods. One hundred university men mostly medical students, living on the campus at the University of Pennsylvania, but coming from various parts of the country furnished the material. Their toes were examined for clinical evidence of ringworm, and after classifying the lesions and recording data on mimeographed protocols the surface of the toe was cleaned and scrapings collected.

These scrapings were prepared for microscopical examination in the usual way by putting some on a glass slide, treating with a few drops of 10 per cent potassium hydroxid, covering with a glass slip, and allowing the preparation to stand for a few minutes, or overnight, before examining under the microscope for the presence of the ringworm fungus. If found, tubes of culture media were inoculated and the ringworm species determined. The following tables record the results of analysis of the protocols.

TABLE I.—INCIDENCE OF CLINICAL RINGWORM.

Number of volunteers examined	100
Clinically positive	67
Clinically negative	23
Questionable*	10

* Some of these were found positive and some negative for fungus on microscopical examination of scrapings.

TABLE II.—DISTRIBUTION OF LESIONS ACCORDING TO TYPE.

	Number.	Per cent of clinically positive patients.
Macerative	68	88
Eczematoid	2	3
Scaly	7	9
Hyperkeratotic	0	0
Total	77	

TABLE III.—ASSOCIATED FORMS OF RINGWORM.

Number of volunteers examined	100
Associated ringworm at present	0
Associated ringworm in the past	14

TABLE IV.—INFLUENCE OF RESIDENCE.

	Number examined.	Number positive clinically.	Number negative clinically.	Number positive microscop.	Per cent positive of total examined.	Per cent positive of cases examined in each section.	
						Clinically.	Microscopic.
East	58	32	26	30	32	55	52
West	1	1	0	1	1		
Middle West	20	10	10	7	20	50	33
South	21	12	9	9	21	57	43

TABLE V.—MICROSCOPICAL FINDINGS.

		Per cent.
Fungus found in scrapings	49	63
Fungus not found in scrapings	28	37
	<hr/>	
Total examined	77	

TABLE VI.—RESULTS OF CULTURES.

		Per cent.*
Positive	5	10
Negative	44	90
	<hr/>	
Total cultured	49	

* Only 49 of the 100 students examined were tested culturally.

Conclusions. 1. Type of Lesion: The macerative (soft corn) predominates—88 per cent of all forms. It is not generally appreciated that this lesion has a fungous connection.

2. Associated Ringworm: From 10 to 15 per cent of those examined had had some other form of ringworm previously.

3. Residence: Much to our surprise this does not seem to have played any part in determining incidence.

4. Incidence: (1) On the clinical basis, that is, from objective symptoms alone, 67 per cent of our student body have ringworm of the toes. (2) On the evidence of the microscope, that is, the discovery of mycelia, 49 per cent were affected. (3) Culturally proven cases number 5 per cent. Certainly the valid figure is higher than this after what has been noted above. The state of vitality, cultural requirements and other circumstances surrounding these mycelia merit further investigation. (4) This disease is by no means one affecting particularly the dispensary class of patients.

5. A Focus of Infection: Most people are unaware that this form of ringworm constitutes a focal infection in relation to the dermatological field just as there are focal infections in internal medicine.

6. Importance: Regardless of the question as to what constitutes ringworm of the feet, and how much symptomatology must exist in order to constitute disease, it still remains as the outstanding feature of the above conclusions, that 5 per cent of our student body harbor living fungi which are known to be the cause of ringworm (as proven by culture), and that from 10 to 15 per cent have had some other form of ringworm previously.

HEART DISEASE AND ABNORMAL ELECTROCARDIOGRAMS.

WITH SPECIAL REFERENCE TO THE CORONARY T WAVE.*

BY HAROLD E. B. PARDEE, M.D.,

NEW YORK CITY.

(From the Second Medical Division of the New York Hospital and the Department of Medicine of Cornell University Medical School.)

THE electrocardiogram is a record of the production of electricity by the heart muscle. This electrical production is one of the functions of the muscle and is intimately connected with the contraction of the fibers. If the muscle is diseased it is not likely to produce the same sort of electric current as when it is healthy, so that the electrocardiographic diagnosis of myocardial disease has become possible through the correlation of special abnormalities of the record, with special types of pathological change. By this means and by animal experiment our knowledge has been increased, so that the electrocardiogram reveals with increasing clearness whether the contraction of the heart is normal or abnormal.

The observation of a patient who showed unusual changes in the, ventricular waves of his electrocardiogram both during and after an attack of coronary artery occlusion, first drew my attention to the possibility that the electrocardiogram might afford a means of confirming a clinical diagnosis of this condition.¹ The characteristic feature was a peculiarity of the *T* wave (Fig. 1) which was very poorly described in the paper in which I originally discussed it. In order to correct this defect in the original paper I would like to state my belief that the significant feature is the presence in one or more leads, usually in only one, of a downward, sharply peaked *T* wave with an upward convexity of the *S-T* or *R-T* interval. If this feature is only present in Lead III it cannot be considered significant unless associated with a downward *T* wave in Lead II, though the downward *T* 2 need not also have this upward convexity preceding the peak.

In the original patient, this peculiarity of *T* persisted for months after the attack. He was lost sight of owing to the war and so an autopsy was not obtained when he died in 1919. In 1918 Herrick published a case with a typical history of coronary occlusion whose record had this same peculiarity of the *T* wave.² This patient came to autopsy and the scar of an old infarct was found in the left ventricle toward the apex. A large number of experiments have been done by Smith upon dogs, and a similar change in the *T* wave of the dog's electrocardiogram was frequently found after tying off branches of the left coronary artery.³

* Presented before the American Society for Clinical Investigation, May 5, 1924.

Many patients with these peculiar *T* waves have come to my attention since the first report, and one of them who was autopsied⁴ was found to have a thrombosis of a branch of the left coronary artery (Fig. 2). Quite recently Smith⁵ reported a case that had the descending branch of the left coronary artery tied to stop hemorrhage and records of this patient showed the typical *T* wave for many weeks.

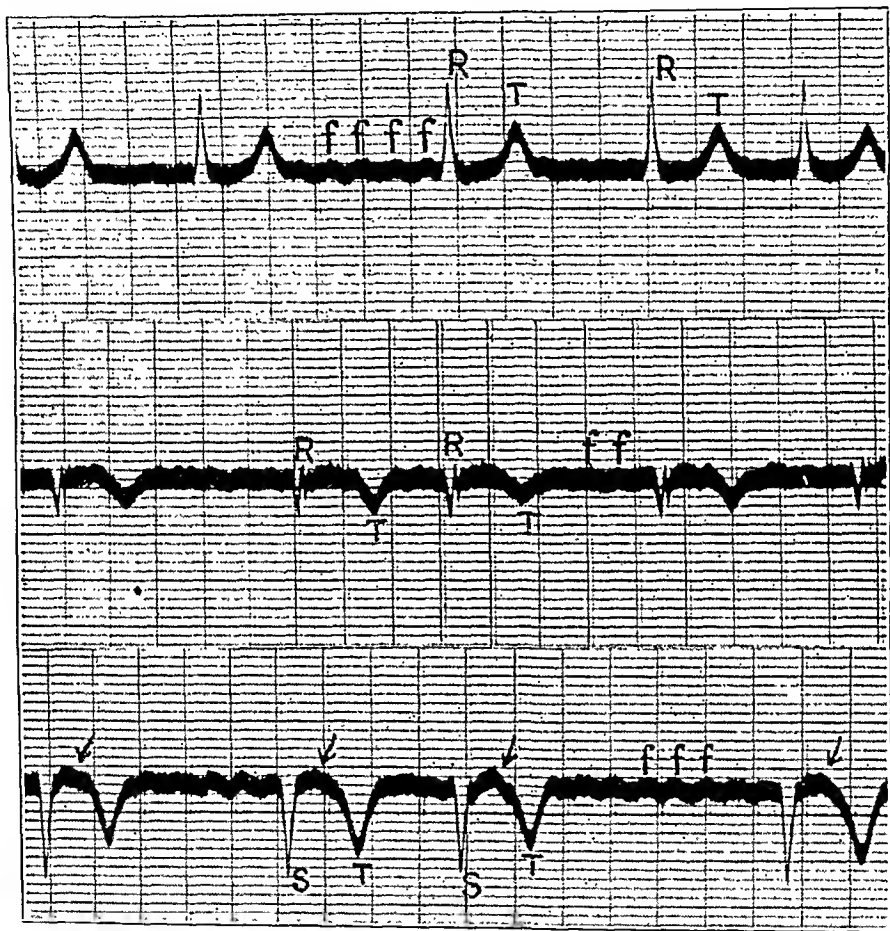


FIG. 1.—Record from a patient who had a thrombosis of a branch of a coronary artery. The characteristic feature is seen in the *T* wave of Lead III; an upward convexity followed by a sharply pointed, downward peak. The record incidentally showed auricular fibrillation by the small wavelets marked *fff*.

It seems as though this peculiarity of *T* might prove to be a reliable physical sign of occlusion of a branch of a coronary artery, and that if its causes could be properly understood it might serve to confirm or deny a clinical diagnosis of arteriosclerosis of the coronaries with narrowing of the lumen. With this in mind I have reviewed a series of 150 adult patients from hospital and private experience, attempting to determine a relation between the clinical features and the electrocardiographic record. Fifty patients were diagnosed as having arteriosclerosis of the coronary arteries, 16

with infarction, 30 with chronic narrowing, and 4 in whom chronic narrowing might have been complicated by infarction. Fifty other patients were diagnosed as having chronic fibrous myocarditis and 50 others, chronic valvular disease.

It is necessary before discussing electrocardiographic findings in these three groups of patients, to give the features upon which the clinical diagnoses rested. Such a clinical grouping can only have value for study when the cases are selected with greatest care and when doubtful cases are rigidly excluded. Coronary infarction was diagnosed when the patient had had an attack of severe sharp pain or a severe heavy pressing pain, felt behind the sternum at a

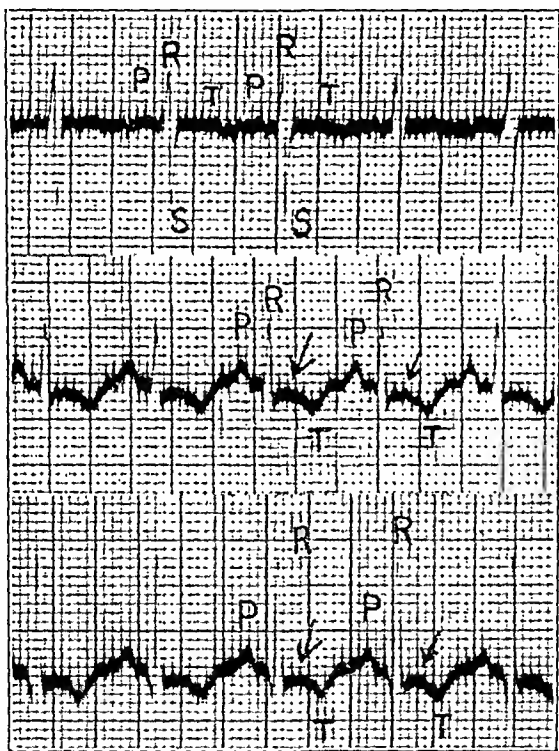


FIG. 2.—Record from a case proved by autopsy. The characteristic upward convexity of the *R-T* interval is seen in Leads II and III.

level between the third and sixth chondrosternal junctions or in the epigastrium. The pain was accompanied by a sense of difficulty in breathing and by marked prostration. The patient was usually covered with cold perspiration, was often nauseated, sometimes vomited and usually eructated gas. The pain usually radiated, though not always, but when it did, passed across the chest to either side or to both, perhaps to the shoulder, especially the left and often down the arm on its ulnar aspect, more frequently to the left arm than to the right. These attacks came on suddenly and without any premonition. They came at a time when the patient was more or less at ease, not usually immediately after an exertion.

He might have been in bed at night, or sitting in a chair after a meal or perhaps moving quietly about his home or place of business.

The picture of coronary arteriosclerosis with chronic narrowing of the lumen is a less clear cut, less definite, but nevertheless clearly recognizable picture. The pain is more easily confused with pains about the heart arising from other causes, so that the term *angina pectoris* applied to vague precordial pains has often been the cause of a wrong diagnosis. We have tried to avoid this error, so that patients were selected for this group only when their symptoms appeared on exertion or with mental excitement. There were attacks of a "pressure" or "heavy feeling" or "lump" situated behind the sternum between the level of the third and sixth chondrosternal junctions, which became a pain if the exertion was continued, and which was severe enough to make it necessary to stop the exertion or the exciting feature. The typical pain is not described as a sharp pain but is dull and heavy. It may radiate to the left shoulder and inner side of the arm and forearm, or more rarely to similar situations on the right side. Rarely there is radiation to the left side of the neck. It is not a steady pain but passes off in a minute or so if the exercise is stopped, returning when it is resumed. Allbutt⁶ has suggested that similar symptoms may arise from disease of the coats of the aortic arch. This may well be the case, especially in the presence of arterial hypertension, but I believe that the pain of aortic disease is not felt below the level of the third rib, and so have excluded from the present group those with pain above this level.

Chronic fibrous myocarditis was diagnosed when the patient had applied for treatment because of symptoms of cardiac failure. Those having valvular disease, or auricular fibrillation or hypertension, or emphysema with chronic bronchitis were excluded, because it was possible that these conditions might have been the cause of the symptoms. Such patients were excluded from this group, for I wished to have as high a percentage of correct diagnosis as possible. A number with myocarditis were probably wrongly excluded, but many more without it were rightly so. The observation of "weak" or "poor quality" heart sounds was not used in reaching this diagnosis for a similar reason. Though these signs are often present with myocarditis, yet they are often found without its being present.

The diagnosis of cardiac valvular disease was only made when typical and characteristic murmurs were heard at the mitral or aortic areas, in patients who sought treatment because of symptoms of cardiac insufficiency. Many of the patients diagnosed as having chronic myocarditis and some in the coronary group had a systolic murmur best heard at the apex and believed to indicate a mitral insufficiency. These were not included in the valvular group, because it was not considered that in adults an uncomplicated mitral insufficiency can cause symptoms of cardiac failure.

TABLE I.

	Coronary occlusion acute and chronic.	Chronic fibrous myocarditis.	Cardiac valvular disease.
Coronary T wave	18	0	0
Downward T in Lead I or Lead II or both	5	10	12
Small excursion of T (low voltage)	0	5	0
Notched QRS group	2	7	0
Small excursion of QRS (low voltage)	3	4	0
Bundle branch-block	6	15	1
Normal QRS and T except for R. V. P. or L. V. P.	16	9	37
Total	50	50	50

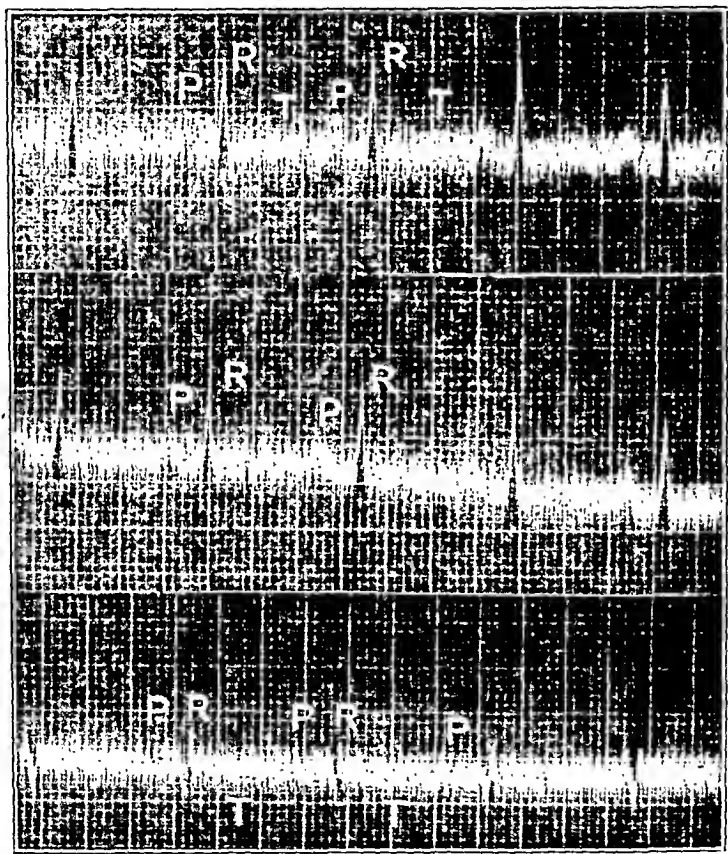


FIG. 3.—Record from a patient with chronic myocarditis. The abnormal feature of this curve is the low voltage of the T wave which is barely perceptible in either lead.

Table I gives a summary of the electrocardiographic findings in these three groups, and a brief word may be appropriate in explanation of what the author has considered significant abnormalities of the ventricular waves.⁷ The coronary T wave has been described above. Downward T wave in Lead I or Lead II or both was only considered significant when the patient was not under the influence of digitalis at the time of taking the record. Patients who had been

taking digitalis within two weeks of the time of the record were not included in this study. Low voltage of *T* (Fig. 3) was only considered significant when the wave failed to reach a height of 0.7 mm. in any lead. Notching of *QRS* (Fig. 4) was considered significant only when it occurred as a definite notch or a slurring in two or three leads and when it was nearer to the peak of the wave than to

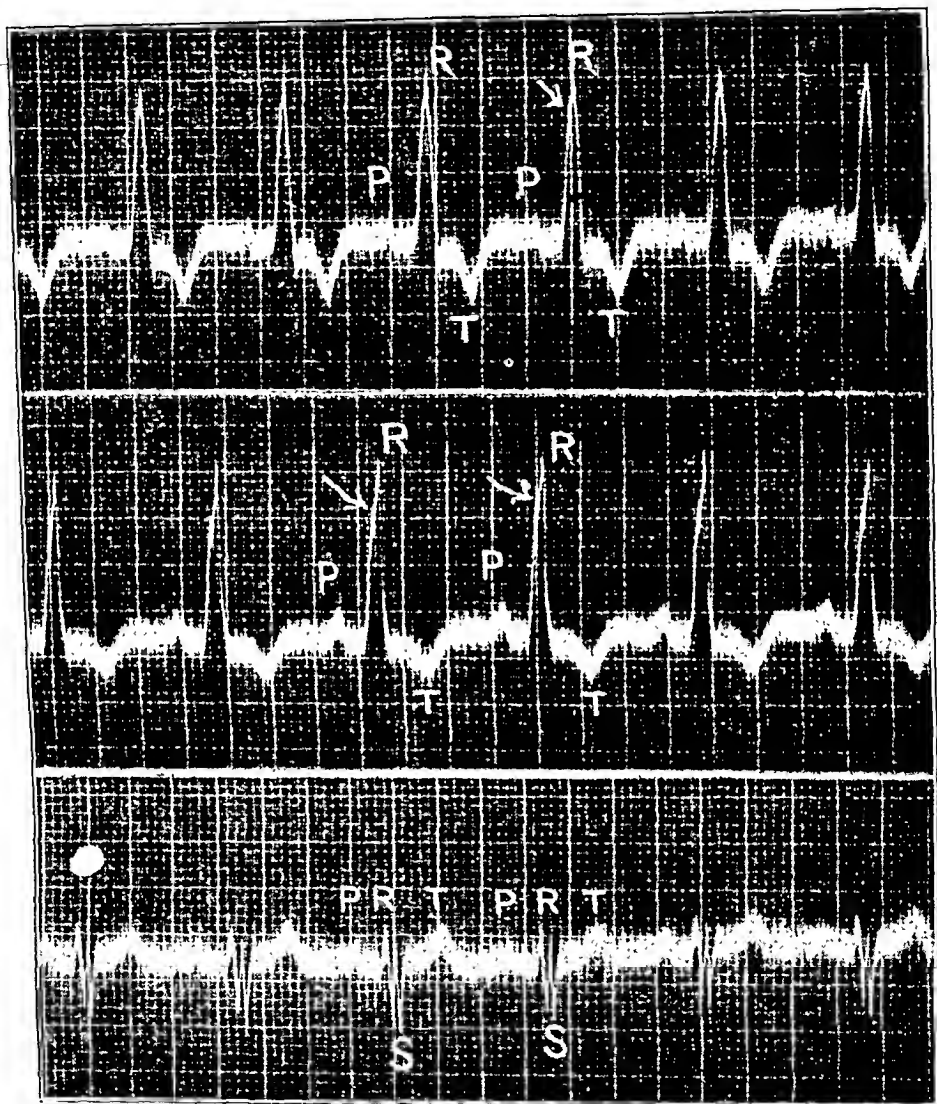


FIG. 4.—Record from a patient with a history of typical pain on effort. This record shows two abnormal features. The notching of *QRS* indicated by the arrow and the downward *T* waves in Leads I and II.

the baseline in the lead giving *QRS* its largest excursion. Notching of *QRS* was always in this series associated with a downward *T* wave in Lead I, Lead II or both, but these records are only reported under notching of *QRS*. Low voltage of *QRS* (Fig. 5) was only considered significant when the maximum excursion in any lead failed to reach a height of 5 mm. Bundle branch-block

(Fig. 6) was diagnosed if the *QRS* group was abnormally prolonged, over 0.14 second, and notched, with the *T* wave oppositely directed to the *QRS* group in its two chief leads.

Some interesting observations were made in these patients bearing on the general significance of normal and abnormal ventricular waves and it will be profitable to consider these before proceeding to the discussion of the coronary *T* wave. We observe in Table I that the great majority of the patients in the myocardial group had abnormal ventricular waves, "bundle branch-block" curves being

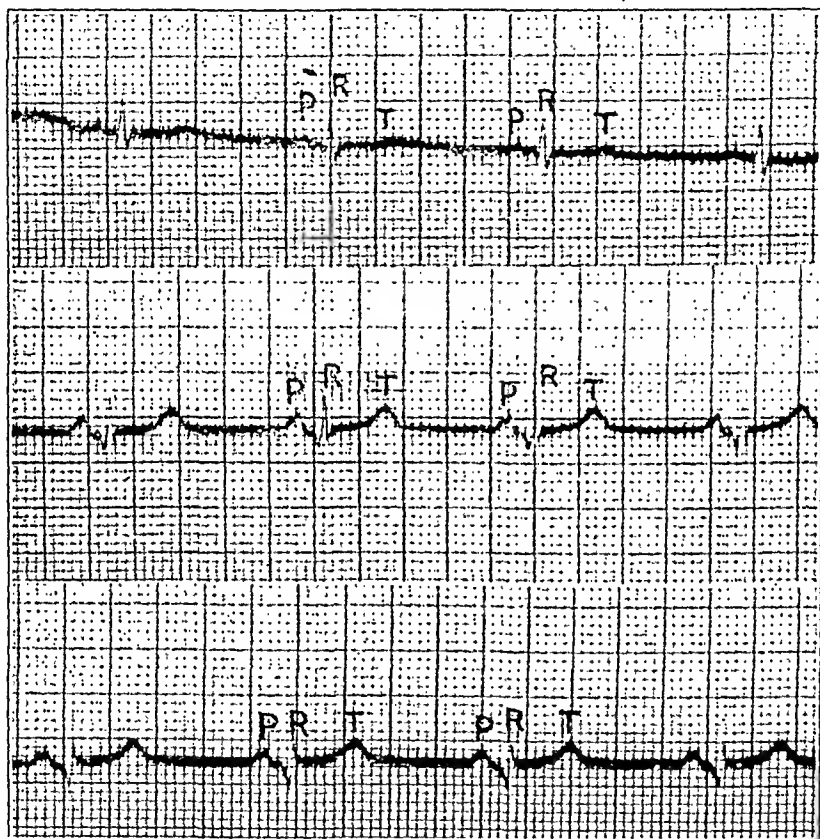


FIG. 5.—Record from a patient with typical pain on effort. The abnormal feature is the unusually low voltage of the *QRS* group.

the most frequent (30 per cent) while downward *T* waves in Lead I, Lead II or both without *QRS* changes were found in 20 per cent. In contrast to this, patients with valvular disease were found to have abnormalities of *QRS* or of *T* rather infrequently. Only 26 per cent of the valvular cases had abnormal waves, and inversion of *T* in Leads I or II was almost the sole type of abnormality. It is interesting to find these electrocardiographic changes so infrequently in patients with disease of the valves, in view of the agreement among pathologists that patients dying of cardiac failure are less likely to have myocardial disease when valvular disease is

present than when it is absent. Evidently valvular lesions are capable of causing cardiac failure, though the process is more easy if the muscle is also affected.

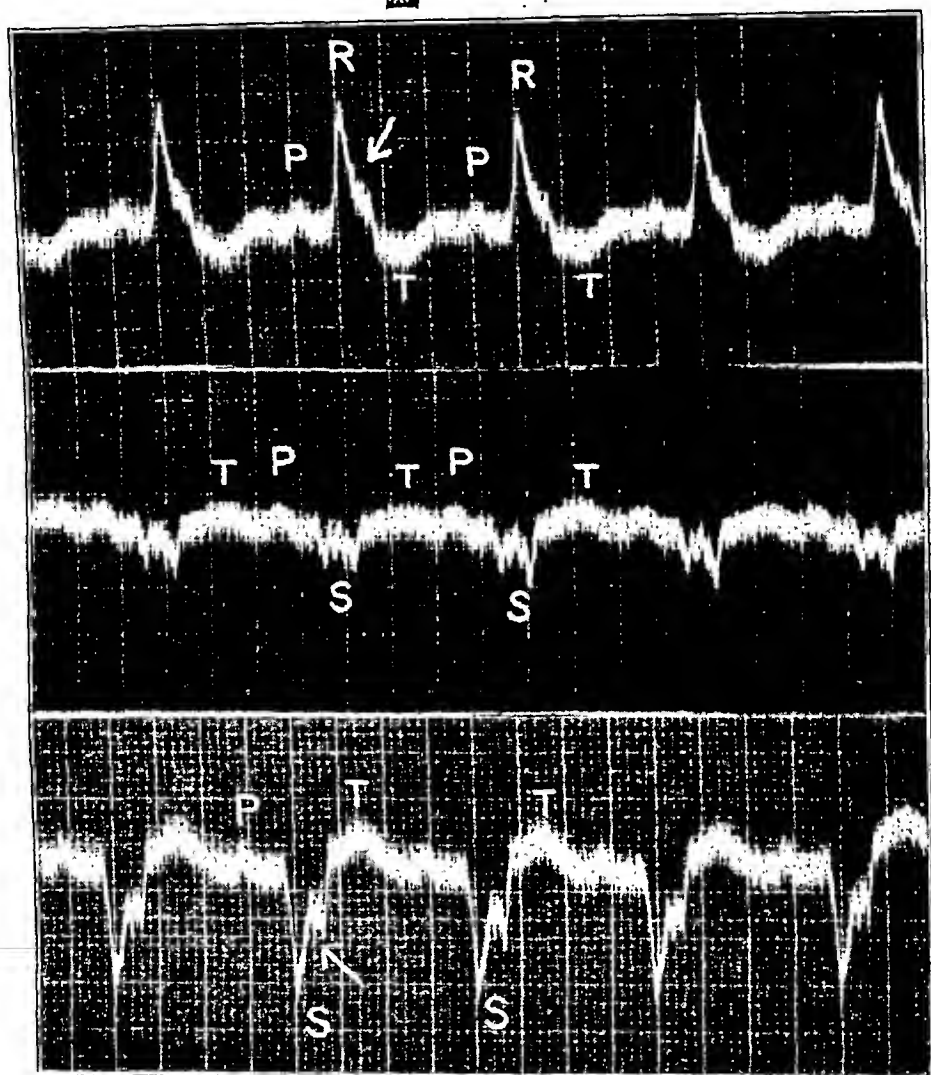


FIG. 6.—Record from a patient with typical pain on effort. The abnormal features of this curve, notching of *QRS* with prolonged duration, and the *T* wave opposite to the *QRS*, give the picture known as bundle branch-block.

TABLE II.

	Total cases.	Normal ventricular waves.		Abnormal ventricular waves.	
		No.	Per cent.	No.	Per cent.
Coronary disease:					
Infarction	16	3	19	13	81
No infarction	30	13	46	17	54
Enlargement	12	4	33	8	67
No enlargement	24	7	30	17	70
Fibrous myocarditis:					
Enlargement	17	2	12	15	88
No enlargement	21	5	24	16	76
Valvular disease:					
Enlargement	27	16	60	11	40
No enlargement	17	16	95	1	5

The important clinical features of these patients were reviewed, the degree of cardiac failure, the character of the pain and the presence of definite, indubitable, cardiac enlargement were each considered in turn. Often the clinical records were unsatisfactory in their statements on these points, so it was not always possible to review each of the cases from all of these aspects.

The degree of cardiac failure at the time the record was taken did not correspond with any special frequency of the abnormal curves we have considered. It is well known to those who see many electrocardiograms that a patient may vary greatly in his cardiac compensation and yet the record may not change in this way. This is usually true of murmurs also for neither the electrocardiograms nor the murmurs are affected in a significant way by whatever it is that determines compensation.*

In all but four of the coronary group, it was possible to decide whether there had or had not been so severe an attack that infarction was likely. In Table II it is seen that of the 16 who had the severe attack, 13 (81 per cent) gave abnormal ventricular waves and of 30 who had not had a severe attack only 17 (54 per cent) showed abnormal waves.

The relation between cardiac enlargement and the finding of abnormal ventricular waves is also shown in Table II. In the coronary group the frequency of electrocardiographic abnormalities in those with and without enlargement was nearly the same, 67 per cent of those with enlargement and 70 per cent of those without it gave abnormal ventricular waves. In the myocardial group 88 per cent of these with enlargement gave abnormal ventricular curves, while of those without enlargement only 76 per cent did so. In the group with valvular disease 40 per cent of those with enlargement had abnormal ventricular waves; but of those without enlargement only 5 per cent (one patient) gave abnormal waves.

It is plain from Table II that with either myocardial or valvular disease the presence of cardiac enlargement makes the finding of abnormal ventricular waves more likely. With coronary disease however enlargement is not an important factor in determining abnormal waves, whereas the occurrence of an infarction is most important.

These observations harmonize with the generally accepted idea that abnormal ventricular waves are due to ventricular muscle disease. It has long been believed that myocardial changes are a most important cause of enlargement, and we see that enlargement and abnormal waves tend to occur together in both the myocardial and valvular groups. The frequency of abnormal waves with

* Although notching or abnormal width of the QRS group and abnormal downward T waves rarely change with the degree of compensation, yet the size of these waves do so quite frequently. Waves will be smaller when the patient is poorly compensated and will grow larger when his condition has improved.

cardiac infarction has the same fundamental cause, for these cases with infarction are the most likely to have serious damage to the ventricular muscle. It must be evident from this how great is the importance of the electrocardiogram in the clinical examination of these patients.

There is a suggestion from Table II that muscle damage may occur without giving rise to abnormal waves, for there were a number of patients who would have been expected to show them but who failed to do so. Two in the myocardial group with enlargement (12 per cent), and 3 in the coronary group with infarction (19 per cent), gave records without any significant abnormality. The infrequency of this occurrence was so slight that it might be partly explained on the ground of mistaken diagnosis, but we cannot deny that the diagnosis was incorrect in all 5 of these patients, so it is impossible to deny that disease may exist in the ventricles without changing the *QRS* or *T* waves in a recognizable manner. How much or how little this disease may be, can only be determined by pathological studies.

It is interesting that of the 62 patients in these three groups who did not show cardiac enlargement, there were 34 who gave abnormal ventricular waves. This suggests that disease of the muscle may often exist without definite enlargement. In such patients the abnormal waves of the electrocardiogram may constitute the only direct physical sign of heart disease, for there may be no enlargement, no abnormality of the heart sounds and no murmurs. These patients are like those with valvular lesions and without definite enlargement, in that their disease has not yet produced the change in the size of the heart which is one of its ultimate results.

The Coronary Group. Considering again Table I we see that 36 per cent of the patients with the coronary diagnosis showed the special coronary *T* wave under discussion. Thirty-two per cent of the coronary group, though failing to have the special *T* wave, yet had some other significant abnormalities of the ventricular waves, so that 68 per cent of these patients had abnormal waves. In the group with fibrous myocarditis not a single instance of the coronary *T* wave was found though 82 per cent showed one or more of the other significant abnormalities of the record. In the valvular group there was no instance of the coronary *T* wave; but 26 per cent of the patients showed abnormal ventricular waves.

The coronary *T* wave seems to be a quite special sort of abnormality of the electrocardiogram occurring in about a third of all patients who give symptoms suggesting coronary narrowing or infarction. It is more frequent in those who have had a more severe attack suggesting infarction, than in those with the milder symptoms of chronic narrowing, being found in 50 per cent of 16 cases of infarction, as against 27 per cent of 30 cases of narrowing.

The pathological basis of this abnormal *T* wave is probably not to be found in the primary anemia of the arterial occlusion, for in dog experiments and in three clinical instances, which I have observed, the primary change has caused a different and quite transient peculiarity of the *T* wave.⁷ The coronary *T* wave here described is probably due to the secondary reaction of repair about the anemic area. On this basis we can understand how it is found in patients who have not gone through the event of an infarction, but who have a slowly progressive narrowing of an arterial branch with a local area of anemia surrounded by the secondary reaction of repair. It is understandable too how the peculiarity might disappear in later records, when the collateral anastomoses have taken over the blood supply of the infarcted area, or when this has been replaced by fibrous tissue.

I have seen this peculiar *T* wave give place to a normal one during a period of nine months, the patient's condition improving the while. A similar return to the normal *T* wave was often observed by Smith in dog experiments, and occurred in the post-operative human heart which he reported. Such a change should be considered to indicate that the affected area has become quiescent, because of a practically complete restitution of function due to the collateral circulation. In patients who continue to have pain on exertion, I have seen this peculiar *T* wave give place to a downward *T* of the usual form without the sharp peak and upwardly convex *S-T* interval. Such a change might be due to fibrotic replacement in the affected area.

That this coronary *T* wave is often due to a lesion in a branch of the left coronary artery is suggested by the fact that 3 of the 4 reported autopsied cases with the special *T* wave (Herrick², Smith,⁵ Pardee,⁴ Wearn⁹) have had the lesion there, and that Smith's post-operative case⁵ which showed the *T* wave had the descending branch of the left coronary tied. It should be remembered in this connection that in 19 autopsied cases, Wearn⁹ found the lesion in the left artery 16 times. The disease is much more frequent in the left artery.

As to the 16 patients in the coronary group who failed to have this special peculiarity of *T* but had other abnormalities of the *QRS* group or *T* wave, it is likely that in these hearts the pathology did not have the special character required to produce this *T* wave, or that having it, the situation of the lesion was such that important branches of the auriculoventricular conducting system were involved. The destruction of important branches of the auriculoventricular system could cause such marked changes in the ventricular waves that the special *T* wave peculiarity would be overshadowed, obviously so if bundle branch block curves resulted. It is possible that in some of these cases that failed to have the typical *T* wave an old infarction had given place to fibrous changes

by the time the record was taken, so that the special peculiarity of *T* which might have been found in an earlier record, was no longer present. The local reaction about the anemic area might have given place to fibrous tissue and the ordinary downward *T* wave was found.

It is significant of the specificity of the pathology underlying the coronary *T* wave, that it did not occur at all in the records of the patients with chronic fibrous myocarditis or with chronic valvular disease.* Those with myocarditis presumably had a more diffuse disease. They showed abnormalities of their ventricular waves with great frequency, but the abnormalities were always some other feature than this peculiar *T* wave.

There were 16 patients in the coronary group, who did not have significant abnormalities of either *QRS* or of *T*. This combination of typical symptoms with a normal electrocardiogram was less common when there was a history to suggest infarction than when the symptoms were those of chronic narrowing (Table II), for of those presumed to have had infarction 19 per cent had normal ventricular waves, while of those with chronic narrowing 46 per cent had normal waves. The presence of normal waves in these 16 patients might arise in one of three different ways: (1) The diagnosis might be incorrect, the patients not having coronary disease at all; (2) the diagnosis might be correct and yet the damage to the muscle be so slight as not to affect the electrical production during systole; (3) there might have been an infarction of a small area which later became revascularized through the collateral anastomoses, so that a previously abnormal electrocardiogram might have given place to one of normal form before our record was taken.

It is of course impossible to say how many of our diagnoses were incorrect, but it is not likely to be as many as 16 out of 50. There must remain a number of patients who had coronary disease with chronic narrowing and even with infarction, and whose normal electrocardiograms are due to the fact that the arterial disease had not yet caused much damage to the ventricular muscle, or that there had been more or less complete restitution of circulation in the damaged area by the collateral anastomoses which have recently been so clearly demonstrated to exist in the heart.⁸

The finding of abnormal ventricular waves in two-thirds of the patients suspected of disease of the coronary arteries has a considerable diagnostic and some prognostic importance. The diagnostic importance is greatest when the peculiar coronary *T* wave is found, for this appears to be due only to a focal area of deficient vascularization, in the ventricular muscle. Other abnormalities of the waves

* I have seen this coronary *T* wave in 2 cases with aortic valvular disease, 1 syphilitic, the other rheumatic, both without cardiac pain. The latter patient is living, the other died without autopsy. I thought that it might indicate involvement of the coronary orifice in the disease.

might arise from a diffuse inflammatory reaction or from the later results of arterial narrowing, or from the results of a widespread coronary disease.

As to prognosis, the finding of the coronary *T* wave indicates coronary atheroma. When this is present the possibility of sudden death from cardiac infarction cannot be denied. On the other hand, as a patient may live for years after a cerebral apoplexy, so here also the fatal event may not be at all imminent. The finding of any other abnormality of *QRS* or *T* with a clinical history of the coronary type must also be looked upon as the result of coronary disease and the possibilities for the future are about as described.

When the patient reveals normal ventricular waves we must make the diagnosis of coronary disease only with a very typical history. We cannot exclude the diagnosis on the ground of normal waves, but we may feel that the arterial condition must be short lived and not of a marked degree, else the muscle would have been sufficiently affected to change the electrical waves. Such a person might be liable to sudden death at this stage of the disease; but it is far less likely than if an electrocardiographic abnormality shows the result of more advanced arterial changes.

Summary. A peculiar form of the *T* wave of the electrocardiogram is described.

The electrocardiogram and certain clinical features of 150 patients were reviewed, their clinical diagnoses being equally divided between coronary artery disease, chronic fibrous myocarditis and cardiac valvular disease.

Eighty-two per cent of the myocardial group, 68 per cent of the coronary group and 26 per cent of the valvular group, showed one or more of the significant abnormalities of the ventricular waves.

The degree of cardiac failure at the time of the record did not coincide with any special frequency of normal or abnormal waves.

The diagnosis of cardiac infarction was associated with a high frequency of abnormal ventricular waves, 81 per cent.

Definite cardiac enlargement was associated with a greater frequency of abnormal waves in both the myocardial and valvular groups but not in the coronary group.

These findings are in agreement with the opinion that the electrocardiographic abnormalities are due to disease of the ventricular muscle.

The special peculiarity of the *T* wave was only found in patients of the coronary group, and only in one-third of these. Another third showed other abnormalities of the ventricular waves and the remaining third had normal waves.

The cause of this coronary *T* wave is considered to be the secondary reaction of repair about an area of deficient blood supply in the ventricular muscle.

The situation of this area is of importance for if the branches of

the auriculoventricular bundle are much involved, other abnormalities of the curve will arise and may mask the special peculiarity of *T*.

The significance of this special *T* wave is discussed and it is concluded that it only arises from coronary artery disease with narrowing of the lumen of a large branch, but that any other abnormality of the electrocardiogram may result from the same cause: If normal waves are found in a patient suspected of coronary disease, we may feel that the arterial changes are not of a marked degree.

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REVIEWS.

PRINCIPLES OF BIOCHEMISTRY. By T. BRAILSFORD ROBERTSON, PH.D., D.Sc., Professor of Physiology and Biochemistry in the University of Adelaide, South Australia; Honorary Consulting Biochemist to the Adelaide Hospital; Formerly Professor of Biochemistry in the University of Toronto. Second edition. Pp. 796; 57 illustrations. Philadelphia: Lea & Febiger, 1924.

THE new second edition of this work, by thorough revision and in parts actual rewriting of the text, is quite abreast of the newest advances in this most fertile field of scientific research. The author continues to keep in mind constantly the close relationship of biochemistry to physiology. This fact together with the author's facile statement of the subject makes the work a particularly valuable one for the medical and premedical student. The physical makeup of the book is a very pleasing one. R. K.

A MANUAL OF PROCTOLOGY. By T. CHITTENDEN HILL, PH.B., M.D., F.R.C.S., Instructor in Proctology, Harvard Graduate School of Medicine; Surgeon to Rectal Department, Boston Dispensary; ex-President, American Proctologic Society. Pp. 279; 84 illustrations. Philadelphia and New York: Lea & Febiger, 1923.

THIS small book makes the usual attempt to present in a small space an adequate consideration of a special subject—considerably more than is found in general text-books or even systems of surgery—and yet leaving out the “excessive details” that fill so many pages of the more exhaustive treatises on the subject. The author seems to have succeeded better than most do in this difficult task. Though the reviewer is not sufficiently familiar with the subject to be an expert critic, it seems as if the author has made an adequate presentation, clearly and accurately, that should be useful both to student and surgeon. Certainly the form of the book and the character of the illustrations leave little to be desired. E. K.

THE PHYSIOLOGY OF EXERCISE. By JAMES HUFF McCURDY, A.M., M.D., M.P.E., Director of Physical Education Course in the International Young Men's Christian Association College, Springfield, Massachusetts; Editor of the American Physical Education Review. Pp. 242; 13 illustrations. Philadelphia: Lea & Febiger, 1924.

THIS book is an excellent statement of the effects of exercise in general, as well as the effects of special types on the bodily functions. It represents not only an ample survey of the literature but the original observations of the author and his assistants over a period of nearly thirty years of active work in the field of physical education. Written primarily as a text-book for students of physical education, it will be found of interest by many others: the physiologist, the cardiologist, and any one who may be only casually interested in the athletic training of youth. R. K.

MODERN METHODS IN THE DIAGNOSIS AND TREATMENT OF RENAL DISEASE. By HUGH MACLEAN, M.D., D.Sc., Professor of Medicine, University of London, and Director of the Medical Clinic, St. Thomas's Hospital. Second Edition. Pp. 110; 8 illustrations. Philadelphia and New York: Lea & Febiger, 1924.

WHEN the reviewer reviewed the first edition of this book his comments were entirely favorable. In looking over the new second edition the same feeling is maintained about this revision as about the first edition. The book presents to the general practitioner a most excellent summary of our knowledge of kidney disease and correlates most successfully the various physiological tests of the function of the kidney with the pathological picture that should be expected as a result of various analysis. The author lays great stress on the simpler examinations which do not require a well equipped laboratory in order to determine the functional condition of this organ. M.

WOMEN CHARACTERS IN RICHARD WAGNER. By LOUISE BRINK, Ph.D. Pp. 125. New York and Washington: Nervous and Mental Disease Publishing Company, 1924.

By applying Freudian principles of psychoanalysis to the women characters of Wagner's "Ring der Nibelungen" the author attempts to analyze Wagner's psychology and purports to find in it an uncon-

seious coneurrenee in Freudian doctrine. On the baek eover, in the price list, of the books of the Nervous and Mental Disease Monograph Series this work is listed at "\$0.00"—a rather apt expression of its probable value, at least to the physician.

K.

THE HENDERSON TRUST LECTURES: No. II. THE STORY OF THE BRAIN. By SIR JAMES CRICHTON-BROWNE, M.D., LL.D., D.Sc., F.R.S. Pp. 28. No. III. PHRENOLOGICAL STUDIES OF THE SKULL AND BRAIN CAST OF SIR THOMAS BROWNE OF NORWICH. By SIR ARTHUR KEITH, M.D., F.R.S. Pp. 30. Edinburgh and London: Oliver & Boyd, 1924.

In these days of the high cost of living, these attractive pamphlets—embodying lectures delivered at the University of Edinburgh during 1924 under a trust founded in 1829—certainly furnish a lot for the money. Written in the lucid, pleasant style so common to British publications—and, alas, so rare in this overpraetieal country—both lectures contain useful as well as entertaining information. In the first is sketched the story of brain function and localization from phrenologists to Pavlov; as to Sir Thomas Browne, Sir William Osler, his diseiple, would doubtless be as surprised as that worthy old mystic himself at the interest that has been taken in him in the past two or three years.

LECTURES ON ENDOCRINOLOGY. By WALTER TIMME, Attending Neurologist, Neurological Institute, New York; Professor of Endocrinology, Broad Street Hospital; Professor of Nervous and Mental Diseases, Polyclinic Medical School and Hospital. Pp. 123; 27 illustrations. New York: Paul B. Hoeber, 1924.

ARTICLES on endocrinology by such a well-known authority as the author are always weleome; it should be stated, however, that this booklet is "an unchanged reprint of the article which appeared in 1921" in the January number of the *Neurological Bulletin*, and that the many contributions and developments that have been made since that time have not been included. While the author's ideas are always interesting and suggestive, it does not seem to the reviewer that the inferences and conclusions drawn are in all cases justified by the actual facts that are available; and yet it is especially in endocrinology that there is the greatest need for a strict segregation of fact from hypothesis or speculation.

E. K.

A LABORATORY MANUAL OF THE ANATOMY OF THE RAT. By HARRISON R. HUNT, PH.D., Professor of Zoölogy in the Michigan Agricultural College. Pp. 123; no illustrations. New York: The Macmillan Company, 1924.

THIS manual was written to supply a guide to the proper dissection of the rat—the easiest mammal to obtain in large quantities for this purpose. The material is carefully and succinctly offered in nine sections—external aspect, the skeletal system, the muscular system, the salivary glands, the vascular system, the respiratory system, the digestive system, the urogenital system, the nervous system. The book should prove valuable, not only for the purpose already indicated, but also in the many laboratories where the rat is used as an experimental animal.

E. K.

CANCER: HOW IT IS CAUSED; HOW IT CAN BE PREVENTED. By J. ELLIS BARKER. Pp. 478. New York: E. P. Dutton & Co., 1924.

THE author, a layman, sets up the theory that all cancer is caused by chronic poisoning. In the intestinal tract chronic constipation with its attendant intoxication is the etiological factor, analogous to the production of cancer of the skin by the prolonged action of coal-tar products. The prevention of cancer can be accomplished by avoiding chronic poisoning—no constipation, no gastrointestinal cancer. Having set up the theory the author tries to fit the facts to it. The reasoning is peculiar, unconvincing and fallacious. The introduction is by Sir Arbuthnot Lane whose writings on intestinal stasis form a chief source of Barker's material and are extensively quoted.

R. K.

GRUNDRISS DER ANATOMIE DES MENSCHEN. By JOHANNES MÖLLER Formerly Prosector at the Vesalianum at Basel and PAUL MÜLLER Formerly Assistant at the Anatomic Institute, Leipzig. Fourth edition. Pp. 493, 91 illustrations. Berlin and Leipzig: Walter De Gruyter & Co., 1924.

SINCE the appearance of the first edition of this little volume in 1902, both its authors have died. The third edition was brought out in 1920 by Professor Broesike. He has preserved the original form of the book attending simply to the elimination of errors and in places clarifying the text. From the standpoint of macroscopic anatomy in particular the book offers a concise, clear outline of the

subject in a convenient and handy form, accounting for the increasing popularity of the book which is now appearing in its fourth edition, less than four years since the issue of the third. . R. K.

OPERATIVE SURGERY, VOLUME V. By WARREN STONE BICKHAM, M.D., and PHAR. M. (TULANE) M.D. (COLUMBIA), F.A.C.S. Former Surgeon in charge of General Surgery, Manhattan State Hospital, New York; Former Instructor in Operative Surgery, College of Physicians and Surgeons (Columbia University), in the New York Post-graduate Medical School and Hospital, and in the New York Polyclinic Medical School and Hospital; Former Visiting Surgeon to Charity Hospital, New Orleans; Junior Surgeon to Touro Hospital, New Orleans; Former Demonstrator in charge of Operative Surgery, Tulane University, New Orleans; Fellow of the New York Academy of Medicine. Containing 6378 illustrations. Philadelphia and London: W. P. Saunders Company, 1924.

VOLUME V deals with surgery of the colon and rectum, the kidney and genito-urinary organs, exclusive of the female pelvis. Classical operations in this field are well described and illustrated. The text and pictures maintain the high standard of excellence established in the previous volumes. It is still the reviewer's opinion that critical comments should be enlarged. This work should be in the hands of all men seriously interested in surgery throughout the country. A little more attention to surgical principles and certain practical phases which underlie surgical judgment would increase its value to many surgeons. D. P.

WHEELER'S HANDBOOK OF MEDICINE. By WILLIAM R. JACK, B.Sc., M.D., F.R.F.P.S.G., Physician to the Glasgow Royal Infirmary, Lecturer in Clinical Medicine in the University, Glasgow. Seventh Edition, pp. 629; 34 illustrations. Edinburgh: E. and S. Livingstone, New York: William Wood & Co., 1924.

THE seventh edition of this excellent little epitome of medicine maintains the standard of previous editions, and, for the most part, gives evidence of careful revision. The only omissions of any importance that the reviewer can find are the following: there is no mention of the intravenous use of mercurochrome or other chemotherapeutic agent in the treatment of septicemia and pyemia; there is no indication of the value of splenectomy in the treatment of purpura hemorrhagica. This book should prove especially helpful to medical students in reviewing for examinations.

F-H.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Intestinal Reductions as Measures of Intestinal Putrefaction.—BERGEIM (*Jour. Biol. Chem.*, 1924, 62, 45) describes a method of estimating intestinal reduction based on the amount of ferric oxide changed to the ferrous form in its passage through the bowel. A definite quantity of the ferric oxide is given, the duration of its stay in the bowel noted and the amount of ferrous form appearing in the feces determined. Calculation gives the rate of the total reduction in the gut. Rats were used as the experimental subjects. He finds that almost all of the reduction takes place in the cecum and large bowel. Those proteins giving rise to increased putrefactions, such as meat and eggs, gave high reduction figures, while casein and milk caused surprisingly little reduction. With the exception of dextrins and lactose, carbohydrates and fats had little effect on the reduction processes. These two carbohydrates, dextrin and lactose, however, produced a characteristic change, the intestinal flora becoming of the acid-producing type and reduction being markedly reduced. Milk alone or with other foods acts markedly to diminish reduction processes, both the casein and lactose apparently taking part in this effect. Fruits and green vegetables also tend moderately in this direction. Anything tending to produce intestinal stasis brings on a markedly increased reduction. Intestinal antiseptics alter the process only temporarily. This measurement of intestinal reduction is held to be indicative of the putrefactive changes going on in the bowel and may be found to be of clinical value in this regard.

Incidence of Spirochæta Pallida in Cerebrospinal Fluid during the Early Stage of Syphilis.—CHESNEY and KEMP (*Jour. Am. Med. Assn.*, 1924, 83, 1725) investigated the spinal fluids of 34 patients with untreated early syphilis by injecting 0.75 to 3 cc of the uncentrifuged fluid into one or both testes of each of 2 normal rabbits, watching for the development of the syphilitic lesion locally or in the lymphatic glands of the rabbits. If nothing was seen after ninety days the testes of the inoculated rabbits were removed, emulsified and reinjected into the testes of other normal rabbits. Only spinal fluids that were normal to the usual tests (cell count, globulin, Wassermann and mastie curve) were injected. All the patients showed signs of secondary syphilis, and all had a positive blood Wassermann reaction. None gave any objective evidence of involvement of the central nervous system. And still, by virtue of the double inoculation tests, the authors demonstrated the presence of the spirochete in 5 of the 34 spinal fluids. In 3 instances the organisms were demonstrated by the first inoculation, and in 2 by the second. Two of the patients with positive spinal fluids had few secondary skin or mucous membrane lesions, while in 3 there was a generalized rash. Four of the 5 patients were females. Whether these findings correspond to the bacteremia found so often in other infectious diseases, or to specific involvement of the central nervous system, is an interesting question.

Relation between Gastric Achylia and Simple and Pernicious Anemia.

—A number of writers have pointed out that achylia gastrica, besides accompanying pernicious anemia, may at times be found to have preceded the onset of the anemia by a number of years. FABER and GRAM (*Arch. Int. Med.*, 1924, 34, 658) record studies on 54 cases of pernicious anemia in an effort to determine the relation between the achylia and anemia. Four of their patients with undoubted pernicious anemia possessed free HCl in the gastric juice. (Faber and Black had also reported 1 such case in a series of 30 pernicious anemia patients.) It cannot be said in these cases, then, that the anemia results from an achylia. In 4 of the authors' series of cases the history of achylia dates back for years (as high as twelve years) before the onset of the pernicious anemia. The deduction is then justified that this achylia cannot be a result of the anemia. Whether it acts to produce the anemia is the important point. HARTMAN (*AM. JOUR. MED. SCI.*, 1921, 162, 201) observed the development of pernicious anemia two or three years after complete gastrectomy, so that the casual factor must lie, not in the absence of free HCl in the stomach, but in changes brought on in the intestines by this HCl lack. Faber and Gram also studied a series of achylia cases in which cancer, tuberculosis and pernicious anemia were ruled out. In 41 per cent of these cases hemoglobin values below the lowest normal values were found. This anemia was more frequent and severe among women than men. The color index was usually lowered, never markedly increased. The anemia is of the simple type and may resemble chlorosis.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Brodie's Abscess.—HENDERSON and SIMON (*Arch. Surg.*, 1924, 9, 504) state that the symptoms of Brodie's abscess are characteristic and may be explained on a pathological basis. It is a focus of infection situated in the spongy portion of the long bones near the epiphyseal line, arising either as a remnant of a former osteomyelitis or of unexplained origin. There is often a period of latency which may be quite long, during which the resistance of the body and the local wall of sclerosed bone at the abscess margin holds the process in abeyance. It may burst into activity as a result of lowered resistance, due in some cases to trauma or acute infection. The occasional complications are: Sinus formation with sequestrum, extension into the diaphysis, effect on general health and marked enlargement. The condition is not tuberculous in origin. Surgical treatment suited to the location in the bone and to the type of abscess results in cure in the majority of cases. Recurrence may occasionally be met with after surgical treatment.

Inflammatory Carcinoma of the Breast.—LEE and TANNENBAUM (*Surg., Gynec. and Obst.*, 1924, 39, 380) say that inflammatory carcinoma appears to be a distinct clinical phase of carcinoma of the breast. Generally this type has been recognized, being frequently mistaken for other diseases of the breast. The inflammatory appearances are characteristic. This variety of mammary cancer shows no constant pathological type. The most striking pathological change is a wide invasion of dermal lymphatics by carcinoma. Bacteriological and biochemical studies have failed to explain the inflammatory manifestations. The cases do badly if treated surgically. At present radiation offers the only hope of palliation, diminishing the patient's suffering and giving a definite prolongation of life.

Malignant Disease of Testicle.—HANDFIELD-JONES (*Lancet*, 1924, 21, 207) says that Jamieson and Dobson's description shows quite clearly that on the right side the glands primarily involved lie on the anterior surface of the inferior vena cava and in the groove between it and the aorta. The dissection must extend from the level of the renal vein to the termination of the common iliac artery. On the left side the glands affected will be to the left of and on the anterior surface of the aorta and bear an intimate relationship to the origin of the inferior mesenteric artery. The extent of the dissection is as wide as that on the right. There is in this radical procedure considerable

danger of rupturing the fragile lymphatics and so seeding the wound with malignant cells, if present. The author compares the results after radical and simple orchidectomy. He feels that it is not practicable and therefore not a justifiable procedure to attempt to remove the lymphatic field. A simple orchidectomy will cure a large percentage of cases if these are seen early enough. The population need educating to the fact that any enlargement of the testicle demands an immediate investigation as to its nature. The author emphasizes the truism that a purely local removal is needed for success while carcinoma and all other forms of malignant disease remain local; but once the disease has begun to spread, surgical procedures no matter how extensive show a very poor percentage of successful cures.

Treatment of Brain Abscess by Unroofing and Temporary Herniation of Abscess, with Avoidance of Usual Drainage Methods.—KING (*Surg. Gynec. and Obst.*, 1924, 39, 554) states that all operative procedures heretofore described in the treatment of brain abscess have been based upon three well-recognized principles—the drainage of the abscess cavity, prevention of extension of meningeal infection and prevention of hernia cerebri. The various operative procedures heretofore described, in which numerous kinds of drainage materials were used usually have been followed by a high mortality rate. In all these procedures described prevention of hernia cerebri has been desired. In this paper the following is advised: Creation of a rather large cranial defect directly over the abscess cavity; complete unroofing of the cavity; Dakinization of area throughout treatment; prevention of trauma and early compression of hernia cerebri; recession of hernia, adhesive strapping and epithelialization. Three cases which were consecutively operated upon and treated in this manner have recovered. There was no mortality in this series of cases.

A Radiological Study of Soft Tissue Tumors.—SUTHERLAND (*Radiology*, 1924, 3, 420) states that there is no definite distinction between benign and malignant tumors. Almost without exception, however, the malignant tumors present homogeneous shadows and the tendency to demarcation is less frequent. They appear in general to invade the tissues more than the benign tumors, but sharp definition of their outline is seen in fibrosarcomas, angiosarcomas and epitheliomas. Melanoepitheliomas show very marked density of their shadows. Lipoma had distinctive findings. Sarcomas were noted with many of the characteristics of the lipoma, while fibrosarcoma may closely simulate neurofibromatosis.

Tuberculosis of the Genito-urinary Tract Confined to the Prostate.—SCOTT (*Jour. Urol.*, 1924, 12, 515) declares that tuberculosis of the genito-urinary tract confined to the prostate, although a rare lesion, does occur. In view of the fact that in the majority of these cases tuberculosis was discovered in the course of the routine pathological studies of the tissue removed at operation, the importance of this procedure cannot be too greatly emphasized. When dealing with patients of the hypertrophy and cancer age, where the diagnosis of either of these conditions seems at all questionable, the possibility of

tuberculosis should not be overlooked in the restudy of these cases. The presence of a previous tuberculous infection of the prostate gland does not necessarily rule out the possibility of a subsequent hypertrophy or cancerous involvement or both.

Plication and Tucking of the Cecum.—HAYNES (*Am. Jour. Surg.*, 1924, 38, 245) states that greatly dilated and elongated cecum is frequently encountered in the course of abdominal operations, especially for appendicular involvement or disease of the pelvic organs in women. The author goes into the etiology at length. The symptoms are usually so masked by the symptoms of the chief organic lesion that leads to operation, that no definite diagnostic points can be presented. There were 2 males and 20 females in the series. The youngest was fifteen and the oldest forty-one years of age. Chronic appendicitis was diagnosed as the chief lesion present in 12 of the patients before operation. In 11 the diagnosis was confirmed at operation and 1 had developed an acute condition of the appendix in the interval between examination and operation. The author describes his technic for handling the abnormal cecum. The results of the operation were uninterrupted convalescence in all cases. Good results were reported in 19 of 22 cases; 1 subsequently had a suppurating molar tooth and mucous colitis. Another showed some enlargement of an ovary that had been conservatively resected for a cystic condition. A third developed a fibroid uterus three years after operation.

Complications following the Use of Mercurochrome-220 Solutions.—WADE (*Northwest Med.*, 1924, 23, 508) declare that it should not be used in deep and poorly drained cavities or sinuses continuously over a long period of time. When indicated in such cases it should be at intervals. When used intravenously it should be given only under urgent circumstances and only then with caution. Strong solutions should not be used until after weaker strengths have first been tried out. Stomatitis may result from the use of weak solutions, 1 per cent solution having produced it.

Sacral Nerve Block Anesthesia.—MEEKER and SCHOLL (*Ann. Surg.*, 1924, 90, 739) find that certain variations of the structure of the sacrum may influence the ease of induction or the result of the anesthetic. The size of the sacral hiatus is variable. In the majority of sacrums the closure of the hiatus is over the fourth, occasionally over the third and rarely over the first or second sacral vertebra. In a small number of cases there is an entire deficiency of the roof of the sacral canal. Palpation of the bony prominences gives the most accurate knowledge of the location of the sacral hiatus and foramina. The postero-superior iliac spines are the most readily accessible bony prominences, and they usually bear a constant relationship to lateral foramina. In the majority of cases the lateral foramina and the contained nerves as well as the sacral hiatus were injected, inducing immediate anesthesia, which is satisfactory in practically all cases. Sacral anesthesia was employed in 1817 cases at the Mayo Clinic. Satisfactory anesthesia was not obtained in 97 cases. The highest percentage of failures occurred in cases in which extrapelvic structures,

not supplied by sacral nerves, were encountered. Sacral injections for therapeutic purposes were carried out in the treatment of nervous conditions and a proportion of cases of sciatica were definitely improved but they were of very little practical value in the treatment of urinary disorders, such as incontinence and enuresis. Anesthesia of the sacral nerves has proved entirely satisfactory for most surgical procedures on the pelvic floor and viscera. It is especially satisfactory in urological cases. The mortality following operations on the bladder, prostate and rectum is markedly reduced by this procedure. Cystoscopic examinations, urethral and bladder manipulations may be readily carried out under sacral anesthesia—a single injection in the hiatus sacralis is sufficient for work of this character.

Fractures of the Hip.—HENDERSON (*Minnesota Med.*, 1924, 7, 786) states that fractures of the hip respond well to treatment, although they do not give the high percentage of good results as do other fractures. They should be reduced and held in position until healing occurs, at least three months, with no weight-bearing for at least six months. The abduction method, advocated by Whitman, has a sound basis. The teaching that non-union is to be expected is in the discard. Careful examination checked up by measurements and roentgen-ray examination at the time of injury will prevent many mistakes. Reëxamination clinically at frequent intervals if roentgen-rays are not made will reveal the ease in which the impaction breaks down. In case of non-union the bone-pegging operation, preferably using the fibula, is the most efficacious. When the neck of the femur is practically gone the reconstruction operations of Brockett and Whitman should be considered. It should be remembered, however, that firm, fibrous union in some instances is quite adequate for the demands of function in the declining years of life. Each patient with non-union of the hip presents a problem that can only be solved by individual study.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Ultraviolet-ray Therapy in Peritoneal and Glandular Tuberculosis of Children.—GERSTENBERGER and WAHL (*Jour. Am. Med. Assn.*, 1924, 83, 1631) present the records of ten cases that were treated in this manner. They found that tuberculosis of the peritoneum and of the mesenteric glands is amenable to treatment by ultraviolet-ray therapy. This peculiarity corresponds in a general way to the experience of the past with other measures used in the treatment of these types, and must be due to some special advantage or characteristic of the lymphatic system of this part of the body. They think that there is no

doubt that the results obtained in these types far surpass in regularity, speed and degree the improvement obtained by rest in bed, laparotomy or soap inunction. Within two weeks the temperature drops and the patient feels and seems better, and usually in about six weeks the temperature has reached normal and there is a marked improvement in the physical signs. The enlarged bronchial glands were also distinctly influenced, as was evidenced by the gradual disappearance of the annoying paroxysmal coughing attacks. The improvement in the bronchial glands was not registered as definitely by the roentgen-ray, which, however, does not negate the definite clinical observation. The peripheral lymph glands also became smaller, but seemingly did not respond as readily to the treatment as did the glands in the mesenteric and mediastinal regions. The use of additional roentgen-ray therapy in these cases of peripheral gland involvement seems to be necessary. Bone lesions seemed to improve under this form of treatment. The treatment does not seem to influence pulmonary tuberculosis, especially of the miliary type. Because of this failure to do good, it seems likely that the good done in other types is due to an indirect and non-specific action, enabling the body in some way to win its own fight against the disease. From the beneficial effect obtained by the use of the ultraviolet rays and also by the administration of cod-liver oil on the calcium metabolism of rickets, and from the old-time conception of the value of cod-liver oil in tuberculosis and of the importance of calcification in the healing process of tuberculosis, it might be imagined that the beneficial effect of these rays in tuberculosis was due to an influence associated with the calcium metabolism in these patients.

Retinal Hemorrhages in the Newborn.—JACOBS (*Jour. Am. Med. Assn.*, 1924, 83, 1637) examined 190 cases shortly after birth in order to discover birth injuries or any anomalies that might appear. The pupils were dilated with a solution of 0.1 per cent of atropin sulphate. Of this series, 157 were examined in the first twenty-four hours of life and 33 were seen after the first day. In 5 cases the cornea was found to be steamy; 3 of these were the children of primipara, 1 of whom had been in labor seventy-nine hours. The condition in at least 1 baby was due to silver nitrate. None of these 5 showed hemorrhages. One baby had a persistent pupillary membrane. This was a seven-month baby who died within twenty-four hours of birth. The vitreous was never found abnormal in appearance in the entire series. There was no paralysis of any extrinsic muscle of the eye. In 1 child, older than twenty-four hours, a nystagmus was found. This was a child that had been delivered by Cesarean section. The retinal picture in all of the series of 157 twenty-four hours or less old showed a fairly frequent increase in caliber of veins. The optic disks were frequently blue-gray in appearance. In such cases the disk border showed no change. Of 22 examined before six hours, 4 showed retinal hemorrhages. Of 34 examined between six and twelve hours, 7 showed retinal hemorrhages. Of 55 examined between twelve and eighteen hours, 7 showed retinal hemorrhages. Of 46 examined between eighteen and twenty-four hours, 1 showed retinal hemorrhages. In 33 patients examined after twenty-four hours there were 4 cases in which retinal hemorrhages were found. Forceps were used in 69 cases. Eight of 19, or

42 per cent, were born with the aid of forceps. Twenty-four hours was the longest period of time of labor in any of these 19 mothers, and there were contracted pelves in 2 of the mothers whose babes showed ocular hemorrhages. The clotting-time of the blood was taken in all cases in which retinal hemorrhage was noted. In no case did it exceed eight minutes, and in most patients it was under six.

Enlarged Thymus.—HARDY (*Michigan State Med. Soc. Jour.*, 1924, 23, 403) used radium therapy in 18 cases of enlarged thymus. In 6 cases untoward symptoms arose after the treatment with radium. In 1 case bronchopneumonia, in an unusually severe toxie form, developed on the second day following the use of radium, and resulted fatally. In another case a week of severe convulsions ensued. Other complications were subnormal temperature and cyanosis; very severe convulsions associated with periods of cyanosis; increase in the cough, periods of cyanosis and suspended respirations occurred during the week following the use of the radium. In 3 cases complete blood counts and non-protein nitrogen estimation was made on the blood before and after the use of the radium. Immediately after the use of the radium a moderate leukocytosis occurred with a small increase in the polymorphonuclears, and an increase in the non-protein blood nitrogen varied. The dose of radium used was that generally employed, 800 mg. hours. In addition to the usual silver filtration. 2 mm. of lead were added to filter out the rays which likely would have caused hyperemias or burns.

Late Serum Immunization in Measles.—REGAN (*Jour. Am. Med. Assn.*, 1924, 83, 1763), in a series of 15 cases, found that under serum immunization the disease was altered. The incubation showed a definite tendency to be longer. The period of invasion was shortened. The coryza was either absent or mild in degree. Koplik's spots were usually absent, or were atypical in evolution. The enanthem was lacking. Prodromal rashes occurred with great frequency. The eruption was altered either in being scant or atypical, and in most instances by becoming ecchymotic as it faded. The temperature curve was distinctly lower. The constitutional reaction was decidedly less pronounced. Complications were practically lacking. The measles convalescent serum, administered late in the incubation period between the sixth and ninth days, and in dosage from 8 to 10 cc, has the property of inducing a mild modified form, which present the alterations in symptoms enumerated above. The reasons that the serum is given late are because the exposure may be known in one case but not in the next. The immunity conferred by an injection early in the period of incubation is probably entirely passive in type. The supply of serum is limited for repeated injections to produce immunization in the same child.

Teeth of Children in Cape Province.—BROWN (*South America Med. Rec.*, 1924, 22, 416) made a survey of the condition of the teeth of the children, and he confirms the theory that a coarser diet is associated with good teeth and a softer diet with bad teeth. It confirms the idea that soft water is prejudicial and hard water beneficial in the develop-

ment of good teeth. It suggests the importance of sunshine in assisting in the growth of good healthy teeth. The use of a tooth-brush is a hygienic measure which is desirable to carry out, but the author believes that it is of secondary importance in the prevention of dental disease. Diet from earliest infancy is the important factor. This should be of a much more detergent character, so that no residue is left behind to undergo decomposition. Coarser meal for bread, crusts, zwieback, raw fruit and raw vegetables, especially of the fibrous sorts are effective cleansing agents. In areas where water supply is soft a greater consumption of calcium containing foods such as milk and cabbage are recommended. It would be advantageous probably to add chalk regularly to the diet. The use of small doses of cod-liver oil and of the greater exposure of the body surface to the sun's rays during the cooler hours of the day, would enable the body tissues to make full use of the available lime in the diet.

Systemic Liver-Spleen Disease.—HANAU (*Monatsh. f. Kinderh.*, 1924, 29, 54) accepts some congenital anomaly as responsible for cirrhosis of the liver when it occurs in children. Abnormal conditions in the spleen follow as a natural consequence, the whole forming the liver-spleen syndrome of constitutional origin. He indicates 30 cases on record with full data, and he describes 4 cases with necropsies in 3. Two were infants, aged two months and twenty-one months; the other a girl, aged fourteen years, and a boy, aged eleven years. The abdomen had been abnormally large in 3 from birth, the liver and spleen large and there had been jaundice during the first three months of life. In the older girl the symptoms had developed at the age of twelve, after three severe attacks of influenza, but improved under roentgen-ray treatment of the spleen. Fourteen months later the condition had become grave again, but the liver was not large this time. The clinical course corresponded to that of fatal Banti's disease, except for speech disturbances and paralysis of the limbs. There were no leukemic changes in the blood or gland enlargement. Necropsy failed to show the etiology unless a tendency to infantilism is accepted as revealing a constitutional element. The boy presented leukopenia, and shifting of the Arneth formula to the left. The extrasplenomegaly dominated the entire clinical picture.

Relation of Sunlight to Spasmophilia and Rickets.—WORINGER (*Rev. de méd.*, 1924, 41, 356) emphasizes the importance of prevention and the definite curative action of sunlight and the ultraviolet ray in spasmophilia and rickets. With special reference to periodic occurrence and geographic distribution, he says that the absence of sunlight is the primary cause of the spasmophilia and rickets, and diet is a secondary factor. The influence of the sunlight is often beneficial to accompanying infections. From the remarkable effect of sunlight the fundamental principle follows that infants should regularly be exposed to it. In densely populated districts and in countries with long dark winters the realization of this is difficult. The mercury vapor quartz lamp affords the most practical solution. A five-minute exposure daily to a 3000-candle-power lamp will suffice for the cure of spasmophilia and rickets, and two, or at the most three, treatments a week would be

sufficient for the prevention. All child welfare centers should be equipped with the quartz lamp, for regular use on all children from the ages of three to eighteen months. This would gradually effect the complete disappearance of these two conditions.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

The Local Wassermann Reaction on the Serum of Chancres from the Clinical Standpoint.—JOSE MAY (*Ann. de Dermat. et de Syphil.*, 1924, 5, 513) reports the result of a local Wassermann reaction done on the serum of 43 chancres, in 25 of which *Spirochæta pallida* were found by dark field, and in 18 of which no *Spirochæta pallida* could be found. The technic employed consisted in the scarification of the lesion after cleansing with distilled water and saline solution. The bloody exudate is aspirated by means of a pipet graduated in 0.01 cc and 0.1 cc, and is mixed with 0.4 physiological saline solution. The mixture is centrifuged and the supernatant fluid after inactivation is used for the Wassermann test. Of the 25 chancres with positive dark fields, the local Wassermann reaction was partially positive twice and strongly positive 6 times. Of the 18 cases with negative dark fields, 6 gave positive local Wassermann reactions. The reaction becomes positive several days before the appearance of a positive reaction in the blood. The occurrence of a negative local Wassermann reaction does not assure against subsequent appearance of a syphilitic infection. The conclusions are essentially a confirmation of those recorded by Klauder and Kolmer (*Arch. Dermat. and Syph.*, August, 1921).

The Skin Manifestations Associated with Leukemia and Allied Conditions.—SIR HUMPHREY ROLLESTON (*Brit. Jour. Dermat. and Syph.*, 1924, 36, 407) publishes a scholarly summary of the cutaneous lesions associated with leukemias, lymphomas and related systemic diseases. He calls attention to the fact that tumor formation precedes the blood changes in Sternberg's leukosarcoma of the skin; a mediastinal tumor, glandular enlargement and infiltration of the viscera precedes the escape of the tumor cells into the blood. He believes that chloroma is related to leukosarcoma, but states that the tumor formation follows the blood changes in the former. Cutaneous changes may be present in the entire group of leukemias and lymphomas as a result of treatment of the primary disease, and may assume therefore the form of pigmentation, keratoses, papillomas and herpes from administration of arsenic; erythema and purpura from benzol; pigmentation and burns from roentgen-rays or radium. These items are not considered at length. The question is raised as to why the skin is selected as a site for tumors in leukemic conditions. It is suggested that auto-agglutination

of white cells occurs in the susceptible skin tissues and that intercurrent infection may be instrumental in initiating the infiltrative process. Leukemic infiltrations are divided into two types: (a) Infiltrations or tumors histologically identical with the primary disease; (b) various non-specific disorders and changes in the skin, such as perspiration, pruritus, pigmentation, prurigo, erythematous, desquamative, vesicular, bullous eruptions, due to toxins, possibly derived from cell destruction in the hemopoietic system. These latter have been called leucemides but the exfoliative erythrodermias are not generally included under this name. Rolleston then successively reviews the diseases in this group individually, with the following comments:

Leukemia. Pruritus is remarkably rare as compared with its frequency in lymphadenoma—only 12 recorded examples—and the author has never seen an example himself. Chronic myeloid leukemia is very rarely accompanied by cutaneous manifestations of any kind, thus contrasting with the rarer disease, chronic lymphoid leukemia, in which a considerable number of cases with cutaneous changes are on record. The question as to whether the cutaneous infiltration is a passive or an active proliferation is still disputed, but Ketron and Gay were unable to find mitoses in a recent series, in opposition to the experience of Arndt and Butler. Cutaneous leukemic tumors, described by Biesiadecki in 1876, are very persistent and seldom come and go. They usually grow slowly and do not ulcerate except rarely, following trauma. In some cases tumors may precede blood changes. They are usually symmetrical; most frequent on the face, scalp, cheeks and eyelids. The leonine aspect may suggest lepra; the slaty blue or plum-color of the nodular lesions may suggest melanotic metastases.

Acute Leukemia. (1) Cutaneous tumors formed of leukemic cells similar to those in the blood, may be seen as in chronic leukemia; they are usually small, and in the acute type do not become confluent; the total white count may not be increased, but the differential count may suggest the diagnosis of an aleukemic acute lymphoid leukemia; the scalp was early involved in Barber's case. (2) Cutaneous eruptions are commoner than in chronic leukemia and are polymorphic. Acute leukemia has many features suggesting an infection. Purpura is almost a constant feature of the disease, probably due to leukocytic blocking of small vessels. Hematomas are easily produced by slight damage. Herpes labialis is a common form of onset. Papules, vesicles, hemorrhagic bullæ, morbilliform exudative erythema and exfoliative erythrodermia may occur. Rolleston has seen no pruritus.

Chronic Leukemia. In chronic myeloid leukemia, purpuric hemorrhages are rare except late in the disease. Multiple evanescent tumors from deep hemorrhages may appear. Jaundice is very rare. Leukemic tumors are in general very rare and may occasionally be limited to the lower trunk

Chronic Lymphoid Leukemia. Livid red infiltration of the face with leonine facies is the commonest form. Confluence is occasional; discrete, small tumor formation, the rule; the process may be universal; the duration of lesions, several years. Differential counts are essential in patients with low total leukocyte counts. Rolleston believes it is only right to designate a lesion as leukemia when the blood quantitatively or qualitatively justifies the diagnosis. Erythrodermias and exfoliative dermatitis are frequent and may be complete, resembling

ptyriasis rubra of Hebra or partial, suggesting psoriasis. Lymphoblastic erythrodermia may occur with moderate leukocytosis and a high relative lymphocytosis. Such cases do not respond to roentgen-ray treatment, which distinguishes them from mycosis fungoides. Pigmentation may occur without the use of arsenic. Urticaria with vesiculation may occur at times, suggesting dermatitis herpetiformis. Sachs reports a pemphigoid eruption lasting two years.

Chloroma. Rolleston believes this to be closely connected with acute leukemia. Tumors occur about the temporal fossa, orbits and skull, and hemorrhages occur into the eyelids, the process suggesting infantile scurvy or hypernephroma. Greenish or brownish discoloration is common with a diffuse olive tint and definite green nodules in the skin (5 in 11 cases).

Multiple Myeloma. Metastatic deposits of calcium may appear in superficial bursae. Pruritus and erythrodermia have been described.

Lymphadenoma (Hodgkin's Disease). From 25 to 39 per cent of all cases present cutaneous manifestations (Ziegler, Cole). Pigmentation may be almost negroid, regardless of arsenic. It may be the sequel of irritation of the sympathetic system by lymphadenomatous glands about the solar plexus, or possible adrenal insufficiency. Jaundice occurs in patients with relapsing fever (Pel-Ebstein syndrome) or from pressure on the bile ducts. Edema of subcutaneous tissues, cyanosis, and atrophy of the skin may result from pressure. The hair may change color or become light, fine and silky. Alopecia may occur with or without pruritus. Excessive perspiration has been observed. Pruritus occurs in 9 to 50 per cent of reported cases. The itching is marked during exacerbations, but the patient must be sometimes questioned to obtain a history of it. It has been insisted upon that eosinophilia and pruritus go hand in hand, but Rolleston has seen high percentages of eosinophils without pruritus. The cause is unknown. Nodular lesions, particularly about the sweat glands, result from chronic scratching. Bullous or pemphigoid eruptions are rare. Universal exfoliative dermatitis has been occasionally reported, but always arouses the suspicion clinically of mycosis fungoides. Morbilliform eruptions, urticaria, erythema nodosum and hemorrhages have been reported. Lymphadenomatous nodules in the skin are quite rare. Lymphadenoma cutis must be distinguished from leukemia cutis by the blood count and from sarcoma and sarcoids.

Mycosis Fungoides. This has been regarded as a cutaneous form of lymphadenoma or as a disease of the hemopoietic system allied both with lymphadenoma and with chronic lymphoid leukemia. Rolleston believes that the histological characters of Hodgkin's are entirely distinct and that a blood count eliminates leukemia. The eczematous, erythematous, premyeotic stage may last for years. It is notable that the tumor formation usually occurs upon the sites of previous erythrodermia.

Two Cases of Skin Manifestations in Leukemic Affections.—ALMKVIST and ARZT (*Brit. Jour. Dermat. and Syph.*, 1924, 36, 428) observe 2 such cases, in 1 of which the ulcerated nodule on the left side of the lower lip clinically suggested a syphilitic chancre, and was associated with slight swelling of the neighboring glands.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

The Abdominal Binder as a Substitute for Pituitrin in the Second Stage of Labor.—BECK (*Jour. Am. Med. Assn.*, 1924, 83, 753) calls attention to the uncertainty in the action of pituitrin. In some patients violent contractions result from moderate doses and in others small doses produce tetanic contraction of the uterine muscles. The fetal heart-beat repeatedly is diminished more than one-half after the administration of pituitrin. In the Long Island College Hospital an abdominal binder of two parts, the upper of canvas with canton flannel lining and the lower part also of canvas made like a many-tailed bandage with buckles, is employed. When this bandage is properly adjusted, it holds the uterus perpendicular to the pelvic inlet, prevents distention of the weaker parts of the abdominal wall, increases intra-abdominal pressure and makes bearing-down efforts more effective. Its use during the second stage of labor and the results have been satisfactory. Comparing 250 primiparous labors with and without the binder, labor was shortened a half hour by the use of the binder; the number of forceps operations was reduced about one-half; infant mortality was lessened about one-third. The danger of uterine rupture is lessened, descent and rotation proceed more successfully and, in multiparous women with relaxed and pendulous abdomens, the binder is of very great value. It must be remembered that the binder is entirely a passive agent. If the patient does not make voluntary efforts at bearing-down, the binder is of no value. It should therefore be used at the beginning of the second stage when the bearing-down efforts are strong. The pressure of the binder may expose the child to some danger. After each contraction of the uterus the lower strap is loosened and the physician listens to the fetal heart. If the child is in danger, the binder is loosened. If the binder sets up too violent labor pains, it should be immediately removed, when such will cease.

The Treatment of Pernicious Vomiting of Pregnancy by Gastric Lavage and Carbohydrate Rectal Feeding.—DENYER (*Brit. Med. Jour.*, 1924, 2, 455) describes the case of a patient two months pregnant who had been vomiting for three weeks before admission to Hospital. The vomitus was green and contained disintegrated blood. The urine was practically normal and the blood-sugar content was normal. The treatment consisted in irrigation of the stomach with sodium bicarbonate solution, 1 dr. to the pint, while by rectum was given 1 pint of water with $\frac{1}{2}$ ounce each of sodium bicarbonate and glucose every four hours. Five minims of adrenalin solution was given hypodermically every three or four hours. The foot of the bed was raised and at night $\frac{1}{6}$ gr. of morphia was administered. As the

patient could retain it, water was given by mouth and glucose was gradually added to the water so taken. Four days after admission the vomiting had practically ceased and the woman went on to recovery. The writer states that adrenalin solution may be given by mouth in doses of 10 to 20 minims in a little water in many of these cases. It is often efficient in stopping vomiting. The addition of 30 gr. of potassium bromide to the solution given by the bowel at evening will help to produce sleep. Adrenalin was used in 1 to 1000 solution.

The Duration of Menstruation and the Development of the Fetus.—SZENES and MONDRE (*Zentralbl. f. Gynäk.*, 1924, 39, 2110) have studied this subject in the Vienna: Clinie 539 cases are the basis of their conclusions and they have illustrated their findings by tables. It was observed that those women who had a longer period of menstruation gave birth on the average to heavier and larger children. If primiparous patients were observed the result was still more striking. While many factors pertain in securing weight and development of a child there is reason to believe that there is a very distinct relation as indicated by the writers, in accounting for what they consider the retention of a greater quantity of nutrient material available for the fetus and also the benefit for the fetus through the greater development of the corpus luteum.

A Roentgen-ray Study of the Infant's Chest at Birth.—WASSON (*Jour. Am. Med. Assn.*, 1924, 83, 1240) publishes a paper upon this subject illustrated with roentgen-ray photographs. The examination was made by having the newborn child subjected to the roentgen-ray immediately on delivery, an exposure of 0.1 second being found sufficient. Exposures are made at intervals of five-ten-fifteen minutes and twenty-four hours after birth, and again before leaving the hospital. In the case of stillborn children, where efforts were made to resuscitate them, some air entered the chest, but a considerable quantity was found in the abdomen and stomach. This method of examination showed that in newborn children before respiration had occurred, that the lungs were uniformly dense throughout. In normal cases the chest expands slowly and the time necessary for this ranges from five minutes to two weeks. The bases of the lungs expand last and the lateral borders first. The shape of the chest changed with respiration, although the lungs before expansion would almost fill the chest space. It is stated that the air capacity of the lung is 17 cc at the end of the first twenty minutes after birth and at the end of six hours, 36 cc. Air enters the stomach and colon of the newborn child at the same time that it enters the lungs. The writer's study shows that it is possible and practical to examine an infant at any age with the roentgen-rays and draw conclusions about the condition in the body.

Pernicious Vomiting in Pregnancy with Low Blood Chlorids and Marked Response to Sodium Chlorid Treatment.—HADEN and GUFFEY (*Am. Jour. Obst. and Gynec.*, 1924, 8, 486) describe the case of a patient, aged twenty years, who had one abortion at two months and during that pregnancy had no vomiting or toxic signs. In the next pregnancy she suffered with pernicious nausea which did not yield to treatment. On

examination of the blood there was a very low chlorid content, there was a carbon dioxide combining power above normal and a moderate increase in non-protein nitrogen, urea nitrogen and uric acid. The patient was given sodium chlorid in one dose of 1500 cc 3 per cent solution subcutaneously, followed on the next day by 500 cc of the same and on the next day by 400 cc or 0.85 per cent. In all 65 gm. of the salt was given in about thirty-six hours. A record of the amount of vomitus showed that it ranged from 850 cc to 400 cc. The blood chlorids after the administration of the salt were still slightly above normal. The blood urea nitrogen had fallen to 12.1 mg. per 100 cc and continued to drop. There was very little chlorid excreted in the urine. The patient's symptoms immediately disappeared and the urine greatly improved. The patient was discharged from the hospital practically well and given sodium chlorid tablets to take. Three or four weeks after leaving the hospital she had an abortion with a macerated fetus. The case suggests that some of the toxemias of pregnancy resemble the toxemia of intestinal obstruction, in such cases sodium chlorid acts in a specific manner.

Chorio-angio Fibroma.—SIDALL (*Am. Jour. Obst. and Gynec.*, 1924, 8, 430) reports the case of a primipara admitted to the hospital in labor with face presentation with spontaneous delivery. The placenta separated spontaneously and on the second day the child developed hemorrhagic condition and was successfully treated by three intra-muscular injections of blood and blood transfusion. Mother and child left the hospital in about three weeks' time. On examination the placenta, the umbilical cord was inserted about 4 cm. from the margin; at the center and in the insertion of the cord was a mass 10 by 7.5 cm. elevated above the surface of the placenta. The tumor was covered by amnion and several umbilical vessels passed across it. It was irregular in contour with nodular elevations and showed through the amnion as a pinkish irregular tumor. The placenta seemed to be normal except at the tumor. On microscopic examination it was found to be a chorio-angio fibroma with fibrous tissues in excess. The writer reviews the literature of the subject and has collected and tabulated 131 cases including his own. There was no relation between the age of the patient and the occurrence of the tumor and there was multiple pregnancy in 5 cases.

Hyperplasia of the Decidua and Hemorrhage at the End of Gestation.—RIOTTE (*Gynéc. et Obst.*, 1924, 9, 23) contributes an illustrated article upon this topic, and cites a number of cases illustrating the clinical history of this condition. From his study of the subject, a true infectious inflammation of the decidua can cause a diffuse hyperplasia of the tissues which will continue with certain variations to the end of pregnancy, and which may become non-infectious as pregnancy proceeds. The cause of this hyperplasia is the excessive development of bloodvessels in the decidua following congenital development of bloodvessels in the endometrium. In other cases this is acquired, but not necessarily infectious. When this hyperplasia is especially developed at the lower pole of the ovum it may give rise to hemorrhage which may influence considerably pregnancy and the course of labor. The cause of these hemorrhages is purely mechanical, and the underlying vascular condition is the important factor.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Radium Therapy of Benign Uterine Bleeding.—WATKINS (*Wisconsin Med. Jour.*, 1924, 23, 123) has employed radium in the treatment of uterine fibroids in 275 cases, and he states that the amount of atrophy which has resulted from radium treatment has been a continuous surprise. Generally there is no diminution in the size of the tumor for three or four months, but after this time the tumor rapidly diminished in size, and in the course of nine to twelve months in many of the cases the tumor had entirely disappeared or had become so small as not to be palpable. Occasionally in such cases small nodules persist for some time. There were 2 cases where the tumor instead of being absorbed underwent cystic degeneration and was excised, and there were 5 or 6 cases where the treatment was repeated once. The author is in accord with the majority of gynecologists in stating that the most delightful results obtained from radium in gynecology is in the treatment of uterine hemorrhages at the menopause. These hemorrhages are probably due to endocrine disturbances, and radium is generally considered a specific for such cases. The technic is the same as for fibroids, except that 1200 mg. hours, double screen, is a sufficient dose. The double screening is used for the purpose of producing a minimum amount of action within the uterus and a maximum amount of action upon the ovaries. The 170 cases of this type which have been treated all have been cured with one treatment. The neurotic disturbances following radium menopause and the natural menopause seem to be much alike, except that they may not persist as long after the radium as after the other. This may be due to the sudden and complete cessation of ovulation after radium treatment. He frequently uses radium and at the same sitting repairs a cystocele or rectocele and the results have indicated that the radium does not interfere with the healing of the wound. In the treatment of leucorrhea he fixes the radium in the cervical canal after thorough dilatation and gives a dose of 100 to 200 mg. hours. He has done this in about 180 cases, and the erosion always heals; the discharge is always improved and has been cured in 80 per cent of the cases. After such a treatment inspection shows very little change in the tissues until after six or eight weeks, then the discharge rapidly diminishes and the erosion heals.

Radiation Treatment of Cancer of the Cervix.—In the beginning of 1922 the American College of Surgeons appointed a committee to study

the results of the treatment of malignant diseases with radium and roentgen-ray, and the treatment of cancer of the cervix was the first subject selected for investigation. The committee collected 1210 case records from twenty-two active gynecological services in various cities and the conclusions reached have been presented by the chairman, DR. ROBERT B. GREENOUGH (*Surg., Gynec. and Obst.*, 1924, 39, 18). He emphasizes the fact that this report is only preliminary, and that it is the purpose of the committee to collect further data and extend the time beyond the minimum period of three years, so that knowledge of the more remote end-results of these cases may be obtained. This report shows that of 829 cases of cancer of the cervix, 94 were free from disease three or more years after treatment. More than half of these "cures" were obtained by the use of radium and roentgen-ray without radical operation. There were no cures by cautery alone. In 243 cases of the early favorable and borderline type hysterectomy alone cured 1 in 3, with an operative mortality of 1 in 5. Radium with palliative operation (cautery) cured about 1 in 3. Under these conditions it may be said that the choice between operation and radium in the treatment of early and favorable cases of cancer of the cervix is an open one. It is to be borne in mind that the results of treatment by radium used with the technic of the present day are not yet available, but that it is generally believed that they will be better than the figures here presented. In more advanced cases the "cures" either by radiation or hysterectomy were very few. The duration of life in the unsuccessful early cases is somewhat greater after radium than with operation, while the formation of rectovaginal and vesicovaginal fistulae occurred with nearly equal frequency with all methods of treatment. Radium, with or without roentgen-ray or palliative operation, was the most important agency in the destruction of local disease in cases which failed to obtain a "cure." The value of radium as a palliative measure in advanced cases is beyond dispute, while in the treatment of recurrent cases after hysterectomy, and in cancer of the cervical stump radium is to be preferred to other methods. A sufficiently large dosage of radium is necessary to obtain destruction of the local lesion; therefore, the treatment of cancer of the cervix with inadequate amounts of radium should not be encouraged.

Endocervical Enucleator.—Enucleation of the mucous membrane and glands of the cervical canal, as popularized by the Sturmdorf type of operation, has come to be recognized as a useful procedure in many types of disease of the cervix, especially in the patient with chronic cervical leucorrhea. SCHLINK (*Med. Jour. Australia*, 1924, 1, 560) has devised an instrument which removes the core of the cervix, quickly and accurately, just going deep enough to include the diseased glands of the canal. The instrument consists of a director staff, armed at its tip with three small tenacula blades. To a sheath fitting over this staff, a circular knife, with an inch-long blade, is attached at a position 2 inches from the concealed tenacula. The knife, by circular rotation, can be made to slip over the director, remaining $\frac{1}{8}$ inch distant from it and completely encompassing the fully extended tenacula blades at the point and extending beyond them for a short distance. In practice

the staff with the tenacula concealed is introduced into the cervical canal to its full extent. The tenacula blades are then extended by a screw at the handle end. This manoeuvre fixes the staff in the cervical tissue, and the circular knife can now be rotated through the cervix. When fully driven home it cuts out a solid 1-inch column of mucosal and cervical tissue to a circular depth of 1 inch. This ensures the whole of the mucosa and a thin strip of muscular tissue being removed. Furthermore, the knife has a limited range of movement, and can do no injury to the bladder or vaginal mucosa; besides it penetrates the inner layer of the cervical musculature, where the vessels are usually small, and gives rise to only a slight amount of hemorrhage which is easily controlled by one or two hemostatic stitches. In addition to performing this operation from below, it can just as readily be performed from above, when, in the course of performing a supravaginal hysterectomy it is deemed advisable to remove the lining of the cervical canal either to remove infected tissue or prevent the later development of carcinoma, without the hazard of performing a panhysterectomy.

Treatment of Ovarian Cancer by Combined Methods.—According to SCHMITZ (*Wisconsin Med. Jour.*, 1924, 23, 125) new growths of the ovary are either clinically or histologically malignant. Ovarian tumors may not show on microscopical examination malignant cells, yet their clinical course may be characterized by ascites and implantation growths on the parietal and visceral peritoneum. The latter finally cause functional death of the peritoneum and death of the patient. The serous papillary cystadenomata are typical examples. About 25 per cent of these tumors and 2 per cent of the pseudomucinous cystadenomata show such a potentially malignant behavior. The discouraging part of these growths is the fact that recurrences after surgical removal amount to about 85 per cent in papillary and 65 per cent in non-papillary growths after they have shown definite cancerous structure. The absolute cures after panhysterectomy for ovarian malignant growths are few in number; the borderline cases are invariably followed by early recurrences, while the inoperable cases are, of course, hopeless. Therefore, the author has instituted in his clinic a postoperative radiation treatment for the three groups of cases. The panhysterectomies are followed by an intensive short-wave length roentgen-ray treatment. The object is to apply a 130 per cent erythema skin-dose homogeneously through the pelvis. The incomplete operations and the inoperable cancers are treated with the combined method of radium and the short-wave length roentgen-rays. Fifty milligrams of radium element are inserted into the uterus until 3600 to 4000 mg. element hours have been applied. The roentgen-rays are applied to two, three or four fields, depending on the size of the patient to obtain a 130 to 150 erythema skin-dose all through the pelvis. Serous papillary and pseudomucinous ovarian cystadenomata causing ascites and transplantation growths in the visceral and parietal peritoneum should be treated the same as the cancers.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

ASSISTANT PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Attempts to Transmit Rheumatic Fever to Rabbits and Guinea-pigs.—Realizing that unsuccessful transmission experiments never prove conclusively the non-existence of a virus in the inocula employed, but appreciating the value of unsuccessful, as well as successful, experimental endeavors, MILLER (*Jour. Exper. Med.*, 1924, 40, 525) reported attempts to transmit rheumatic fever to rabbits and guinea-pigs by injecting them with various materials obtained from patients suffering with this disease. Twenty-seven rabbits and 14 guinea-pigs received one of the following materials: Whole blood, serum, joint fluid, pleural fluid, throat washings and suspensions of tonsil tissue. Subsequent transfer inoculations from animal to animal brought the total number of animals employed in the experiments to 67 rabbits and 40 guinea-pigs. One rabbit, receiving blood and suspension of heart muscle from a rabbit inoculated with whole blood from a patient with rheumatic fever, and 1 guinea-pig, injected intraperitoneally with 3 cc of filtered throat washings from a patient with rheumatic fever, developed an acute non-bacterial arthritis. No other evidence of successful transmission of the disease was obtained. In about one-half of the rabbits and two-thirds of the guinea-pigs myocardial lesions were encountered, which consisted of interstitial accumulations of lymphocytes and endothelial cells. Similar lesions were found in control animals. This last observation furnished the text of a companion paper by the same author (*Jour. Exper. Med.*, 1924, 40, 543), in which he reported the occurrence of myocardial lesions in 20 (60 per cent) of 34 apparently healthy rabbits, whose hearts were studied microscopically. The lesions consisted of lymphocytes and endothelial leukocytes in varying proportions, to which were sometimes added polymorphonuclear eosinophiles, plasma cells and fibroblasts in small numbers. The lesions occurred most frequently between the muscle fibers of the papillary muscles and ventricular walls, and occasionally beneath the endocardium and epicardium. No microorganisms or cell inclusion bodies were found in the lesions.

Occurrence of Bacillus Botulinus in Human and Animal Excreta (XXI).—EASTON and MEYER (*Jour. Infect. Dis.*, 1924, 35, 207) reported the findings made on human and animal excreta collected in California during the years 1920–1922. Their results confirmed the previous conclusions of these investigators (*Jour. Infect. Dis.*, 1922, 31, 544), namely, that animal manure or human excreta is of little or no importance in the distribution of *Bacillus botulinus*. Eighty-eight stool specimens,

obtained from healthy persons from three different parts of California, failed to yield *Bacillus botulinus*, although it was known that spores of this anaërobie had been ingested on the raw vegetables and food which served as food. Three hogs and 2 cattle specimens, or 5 out of 50 samples of animal excreta collected in widely separated areas of California from hogs, cattle, horses, sheep and chickens, contained *Bacillus botulinus*, Type A. From their investigations the authors conclude that "The evidence secured from an examination of 95 manure specimens strongly indicates that animal excreta contributes relatively little to the pollution of the soil with *Bacillus botulinus*."

Observations on the Presence of a Toxic Substance in the Blood and Urine of Patients with Scarlet Fever.— "Recent studies by Dochez, Mair, and Diek and Diek have indicated that scarlet fever may be regarded as a local infection of the throat by a special type of *Streptococcus hemolyticus* which is capable of producing a soluble toxic substance. It is supposed that this toxic substance is absorbed from the throat and causes the general manifestations of the disease. Whether this substance is a true exotoxin similar to diphtheria toxin has not as yet been established. It is supposed, furthermore, that immunity to scarlet fever, whether existing in a normal individual or acquired by an attack of the disease is antitoxic in nature and that the presence of immunity can be determined in an individual by finding out whether or not he reacts to an injection of the toxic substance found in filtrate of scarlatinal streptococcus cultures." In order to provide further evidence in support of the foregoing conception of scarlet fever, TRASK and BLAKE (*Jour. Exper. Med.*, 1924, 50, 381) conducted a series of experiments to determine whether a specific toxic substance could be demonstrated in the blood and urine of scarlet-fever patients during the acute stage of the disease. In order to accomplish this samples of venous blood were collected from patients acutely ill with scarlet fever, and the sterile serum was stored without preservative. Specimens of urine were filtered through Berkefeld filters and stored in a similar way. Tests for the presence of a toxic substance in the serum and urine samples were made by intracutaneous injections in two groups of human volunteers. Members of the first group were supposedly susceptible because their serums failed to blanch the rash in patients with scarlet fever. Members of the second group were supposedly insusceptible because their serums blanched the rash in patients with scarlet fever. After divers ingenious experiments it was found that a toxic substance could be demonstrated in the serum by means of intracutaneous injections of the serum in persons who had not had scarlet fever and whose serums failed to blanch the rash in scarlet fever. The reaction caused by this substance consisted of a bright red local erythema, varying from 20 to 70 mm. in diameter, of one to four days' duration. The severer reactions were moderately indurated and tender, and were followed by pigmentation and desquamation. Control injections in persons whose serums blanched the rash in scarlet fever caused no reaction. The toxic substance was not neutralized by mixture with a human serum which gave a negative blanching test, but was readily neutralized by a human serum which gave a positive blanching test. It was not neutralized

by normal horse serum, but was completely neutralized by Dochez's scarlatinal antistreptococcus serum. In a limited number of observations on the urine of patients with scarlet fever a similar toxic substance was found in 2 out of 5 cases studied. Since the toxic substance described appeared to resemble the toxic substance found in the filtrates of scarlatinal hemolytic streptococcus cultures by Dick and Dick, and since it is neutralized not only by a blanching human serum but also by Dochez's scarlatinal antistreptococci horse serum, the authors feel that the experiments reported support the conception that scarlet fever is a local infection of the throat by a particular type of *Streptococcus hemolyticus* capable of producing a toxin which is absorbed and is the cause of the general manifestations of the disease.

Studies on the Biology of Streptococcus: III. Agglutination and Absorption of Agglutinin with Streptococcus Scarlatinae.—Recent studies of the group of hemolytic streptococci associated with scarlet fever indicate that the individual strains are closely related antigenically. These organisms are present in the early stages of the disease in the throats of practically all individuals suffering from scarlet fever. In addition, the specific streptococcus has been isolated from the uterine secretions in an undoubted instance of puerperal scarlet fever, from the wound in a case of wound scarlet and from the local lesion in an instance of scarlet fever due to infection of a burn, as well as from infected milk and from patients in a milk-borne epidemic of scarlet fever. With the hope of discovering additional evidence, STEVENS and DOCHEZ (*Jour. Exper. Med.*, 1924, 40, 253) again employed the agglutination and absorption of agglutinin reactions to various strains of *Streptococcus hemolyticus* from the throats of scarlet-fever patients in New York, Baltimore, Chicago, Copenhagen and San Francisco. The cultures were obtained, usually, during the early days of the disease. The technic of cultivation and agglutination was the same as previously described by Dochez and others. The immune serum was prepared by inoculating rabbits intravenously first with heat-killed and then with living broth cultures. After extensive experimentation it was found that the strains of hemolytic streptococci from the various cities interagglutinated with immune sera prepared with these strains; that sera prepared with these strains did not agglutinate pyogenic streptococci or strains isolated from cases of septic sore throat; that the strains obtained from the throats of patients from an epidemic of scarlet fever and the strain from the milk responsible for this epidemic fell into the scarlatinal group according to the agglutination tests, and that a group of hemolytic streptococci biologically distinct from streptococci from other sources than scarlet fever was constantly associated with scarlatina. In a subsequent communication, these authors (*Jour. Exper. Med.*, 1924, 40, 493) reported further studies on the distribution of the *Streptococcus scarlatinae*, as identified by agglutination reactions, in the throats of individuals with acute scarlet fever, during convalescence and in the complications of scarlet fever. It was learned that a group of streptococci which agglutinate with scarlatinal immune serum could be isolated from the throats of 65 per cent of cases of scarlet fever during the first week of the disease; that strains of hemolytic streptococci belonging to this group could be

isolated from the throats of patients at the termination of quarantine (thirty days); that hemolytic streptococci were found most frequently in the throat in convalescent patients in whom the tonsillar inflammation had not subsided entirely and that the complications occurring in scarlet fever could be due to the original scarlatinal strain or could result from a secondary infection with pyogenic strains of streptococci.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. MCCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

The Mental and Nervous Side of Addiction to Narcotic Drugs.—WHOLEY (*Jour. Am. Med. Assn.*, 1924, 83, 321) states that habit-forming drugs produce different and more complicated pathological changes than those produced by other toxins and infectious agents. Morphine produces its most serious effects through its action on the vegetative nervous system. Habit-forming drugs induce a distortion of normal reflex activities in both sensory and psychic spheres. The substitution of a psychopathic status is maintained by increasing the obtunding drug to offset the ever decreasing compensatory efforts of the organism. Because of the overwhelming dependence of instinctive and emotional life on visceral and endocrine functioning, instinctive and character deviations follow prolonged disturbance of their activities with more or less permanent changes resulting in the entire personality. This mechanism is the essential lesion in narcotic addictions. The theory suggested supplies a basis for the understanding of narcotism on which the entire symptomatology can be adequately explained.

Production of Immunity by Inhalation.—STILLMAN (*Jour. Exp. Med.* 1923, 38, 117) in a paper which appeared a year ago showed that following inhalation of virulent pneumococci they generally disappear from the lungs of normal mice within a few hours, that infection rarely occurs, and that in only a few instances does death result from a septicemia. The regularity with which pneumococci may be recovered from small pieces of lung is evidence that the organisms enter the lower respiratory tract. Despite the presence of virulent organisms deep in the respiratory tract the animals are only infrequently infected, as evidenced by the large number of survivals. Furthermore, since the organisms are only found in the lungs for a few hours after inhalation there must be an efficient method for their disposal. If mice are first intoxicated

with alcohol and then sprayed with pneumococci by the same technic, the pneumococci persist in the lungs for much longer periods and fatal septicemia occurs in as many as 40 per cent of the mice. Evidently alcohol interferes in some way with the mechanism concerned with the disposal of inspired bacteria. No evidence was obtained, however, as to the exact method of this disposal. If the removal of the bacteria is accomplished solely by the action of the ciliary currents, that is, mechanically, one would suspect that no immunity would be acquired, as the respiratory tract is really "outside the body." If on the other hand, the inspired bacteria penetrate the surface epithelium and actually gain access to the lung tissue proper, some degree of immunity might reasonably be expected to develop. The results obtained by WEBSTER (*Jour. Exp. Med.*, 1923, 37, 231) on microbic virulence and host susceptibility in mouse typhoid infection are strikingly paralleled by the results obtained by STILLMAN (*Jour. Exp. Med.*, 1924, 40, 567). Webster found that if he fed 100 mice 6,000,000 typhoid bacilli by stomach tube, approximately 70 died with the organism in the blood and stools, and 30 survived. In 20 of the latter typhoid bacilli were present in cultures from the stools only during the first few days and not in cultures from the blood—in which respect these animals were naturally immune—while in the remaining 10 animals the organisms persisted in the stool sometimes as long as six months and were temporarily present in the blood stream. Such animals recovered and developed agglutinins. The second group mentioned represent animals which develop an acquired immunity after passing through the so-called "carrier state" or condition of "latent infection." CECIL and STEFFEN (*Pub. Health Rep.*, 1922, 37, 2735) were able to show that intratracheal injections of killed cultures rendered monkeys insusceptible to later intratracheal injections of living pneumococci. They were unable, however, to produce any immunity by spraying killed cultures into the pharynx. Although JONES (*Jour. Exp. Med.*, 1924, 39, 725) could immunize rabbits against *B. arisepticus* by the intratracheal injection of killed cultures, he was unable by means of sprays of heat-killed organisms to increase the resistance appreciable. He concluded that in the latter instance insufficient antigen was absorbed to afford measurable protection against subsequent intratracheal infection. From the foregoing experiments it appears that a high degree of active immunity is produced in mice following repeated inhalations of living pneumococci, and that a less marked increase in resistance is afforded animals exposed to a spray of dead organisms. To explain this acquired protection, one is forced to assume that the inhaled bacteria or bacterial cells actually gain access to the body tissue, that is, they are not only implanted on the mucosa of the lower respiratory tract, but actually penetrate the respiratory epithelium. Very few living organisms probably gain entrance at any one time. In fact, Stillman has never observed pneumococci in histological sections from the animals, while even culturally it is not sufficient merely to inoculate a blood agar plate with the cut surface of the lung tissue, for so few are the organisms present that sections of the tissue itself must be cultured in broth. Even under these optimum conditions growth is not infrequently delayed until after twenty-four hours. One may suppose the high degree of active immunity which results from the inhalation of live organisms to be due to the limited multiplication of

the organisms within the tissue. The possibility exists, however, that actual multiplication of the pneumococci does not occur but that mice may be immunized to a fairly high degree by the repeated penetration of a very few virulent organisms which are quickly destroyed. Stillman concludes that a definite degree of active immunity can be induced in mice through the repeated inhalation of live pneumococci. Only slight immunity is induced in mice by the repeated inhalation of killed organisms.

Thyroid Survey of 47,493 Elementary School Children in Cincinnati.—OLESON (*Pub. Health Rep.*, 1924, 39, 1777) discusses the object of a thyroid survey, and methods for determining the extent of thyroid enlargement, suggests standards for recording thyroid enlargement, and recognizes the following degrees of enlargement: Very slight, slight, moderate, marked, very marked, and adenomas. The percentage of enlarged glands found among 23,710 boys was 26.6 per cent; among 23,783 girls was 39.8 per cent; and by combining the sexes the percentage was 33.2 per cent. The percentages were a little higher for colored than for white children. But one definite case of exophthalmic goiter was found. The necessity for public health effort in the way of goiter prevention is stressed, the treatment of course being reserved to the physician. The author believes that iodine prophylaxis is often entirely overlooked; the administration in the form of iodized table salt is recommended, as the author believes this to be effective and regards the objections to it as not of great weight. It is suggested that a Federal statute should require table salt to contain a certain amount of iodine.

Results of Toxin-Antitoxin in Suppressing a Diphtheria Epidemic.—LAIDLAW (*N. Y. State Dept. Health Quart.*, 1924, 1, 73) recommends that a toxin-antitoxin campaign be instituted upon the appearance of diphtheria in any community. He states that while practically no effect can be expected upon the case rate for two months, after that time sufficient results may be expected to justify the effort expended, and a decided effect may be produced upon the increased incidence after the subsiding of the outbreak. Some degree of modification of the severity of the disease may be expected as early as three weeks. Three doses of toxin-antitoxin cannot be expected to immunize every individual.

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All communications should be addressed to—

DR. EDWARD B. KRUMBHAR, The Laboratories, Philadelphia General Hospital, Thirty-fourth Street below Pine.



(Photo by Richard T. Dooner, Phila.)

JOHN H. MUSSER, JR.

AN APPRECIATION.

DR. JOHN H. MUSSER's removal to New Orleans to accept the chair of medicine at Tulane University has necessitated his resignation as Editor of this Journal, thus terminating a ten-year connection. Appointed Assistant Editor in 1914, under Dr. G. M. Piersol, Dr. Musser continued in this position until on Dr. Piersol's resignation in 1922 he became the Editor—the ninth to hold this position in 105 years. The previous editors were Nathaniel Chapman, 1820; Isaac Hays, 1833; I. Minis Hays, 1879; E. P. Davis, 1891; Alfred Stengel, 1899; F. R. Packard, 1901; A. O. J. Kelly, 1906; G. M. Piersol, 1911.

In spite of his numerous institutional duties and the ever increasing demands of a rapidly growing practice, he always found time to do more of the editorial work than his associate editor thought proper. The eight-hour working day, however, was literally almost doubled in the process, and the time necessary for first-class scientific work became more and more difficult to obtain. At Tulane, on the other hand, as full-time head of an important department of a progressive school, Dr. Musser should have ample opportunity to render a splendid service to medical education, as well as to satisfy his own intellectual requirements. Much as his Philadelphia friends will miss him, they must recognize that his recent decision was a wise one. During Dr. Musser's editorship, the policy of the Journal continued with very little change. His constant attention to possible improvement in the form of its contents and the quality of the English used in its articles was not without results—a trend in a direction for which there is still much room for improvement in American medical literature.

In the first number of the Journal (*The Philadelphia Journal of the Medical and Physical Sciences*, 1820, 1, 1), its editor, Nathaniel Chapman, thought it necessary to quote from the Edinburgh Review: "What does the world yet owe to American physicians and surgeons?" as a reason for his venture. Though an unfair criticism even then, certainly it is not one that would even be suggested today. And yet the present editors feel now as much as then the necessity, in the words of Chapman's prospectus, "to evolve and stimulate the genius of the country to invigorated efforts . . . We look to the profession at large for countenance and support of a scheme that deeply concerns the whole, and which we are sensible can only succeed by general appreciation and cordial coöperation." If this can be secured, we have high hopes that we can succeed in maintaining it, even in the face of the rapidly changing conditions of medical journalism in this country, as Sir William Osler said, "one of the few great journals of the world."

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ORIGINAL ARTICLES.

REFLECTIONS ON THE INTERPRETATION OF SYSTOLIC
CARDIAC MURMURS.*

BY WILLIAM S. THAYER, M.D., F.R.C.P.I. (Hon.),
BALTIMORE, MD.

THE art of prognosis with which the insurance examiner is especially concerned, is one of the most important branches of medicine.

But unless prognosis springs from solid diagnostic roots the tree is unstable.

The art of prognosis may, under some conditions, depend largely on the consideration of figures and statistics based on scientific analyses of accumulated observations.

The art of diagnosis must always depend, in large part, on the observation, the care, the skill, the intelligence and the reasoning power of the individual examiner.

The ability and the reliability of the individual examiner, on the results of whose reports conclusions are to be reached, constitute the corner stone of the prognostic art.

As one who has, for many years, been especially interested in diagnostic problems, and has taught physical diagnosis off and on for thirty-four years, it is naturally from the diagnostic standpoint and from my own experience rather than from a review of the literature that I shall approach this subject.

In what is rapidly becoming a fairly long experience, I am rather impressed with the frequency of what seems to me an unfortunate attitude of student and physician in approaching certain diagnostic

* Remarks made before the Medical Section of the American Life Convention at Atlantic City, June 4, 1924.

problems. We hear, let us say, a modification of a heart sound. We make note of a "systolic murmur at the apex;" and forthwith the mind jumps to a consideration of cardiac murmurs in the abstract before we have given sufficient thought to the vital question, which only we can decide intelligently, namely, what may be the cause of this particular sound in the concrete case.

If we are incapable of exercising our reason on the basis of simple anatomical, physical and physiological considerations, not all the statistics in the world can make us intelligent or competent diagnosticians. Too many accept the statements of others; too few reflect for themselves on the simple physical conditions on which a cardiac murmur may depend.

I am, for instance, impressed by a statement that appears on page 10 of your excellent little pamphlet *à propos* of systolic murmurs in the second right space: ". . . in older applicants (they) may indicate arterio-sclerotic roughening at the aortic orifice."

It is never safe to make positive assertions in medicine. I am, however, not aware that evidence has ever been presented of the origin of any of these common murmurs, other than those dependent upon a true stenosis, from "roughening" at an orifice. An adequate explanation of the origin of such murmurs is not difficult to find. But the true explanation, I venture to fancy, has nothing to do with a "roughening" of the orifice, which, as a matter of fact, excepting in stenoses, is not found anatomically.

Let us for a moment reflect on some of the conditions associated with the origin of systolic murmurs.

Reduced to its simplest terms the "constatation," as the French say—an admirable word meaning observation with appreciation for which I know no equivalent in English—the constatation of a systolic murmur at some point in the circulatory apparatus means the presence of audible vibrations of the vessel wall resulting from the passage of blood from a narrower suddenly into a wider cavity, or through a constricted area in the course of the tube. Whatever the physical possibilities as to the origin of vibrations in fluid currents, it is doubtful whether murmurs that are clinically appreciable ever arise in another way.

The manner of origin of a murmur may be illustrated simply and satisfactorily by pinching a rubber tube through which water is flowing. Beyond the point of constriction there arise a palpable thrill and an audible murmur, appreciable only when the current becomes of sufficient rapidity. This murmur is transmitted in the course of the current; it is but feebly heard back of the point of its origin. Other things being equal, murmurs arise more readily in thin fluids of low viscosity and specific gravity, flowing at a high rate of velocity.

When one considers the structure of the heart there are certain points at which one might expect murmurs to arise in the ordinary course of events. Such points are notably the *aortic* and *pulmonic*

were rings. These rings, fibrous structures, more or less constant in their circumference, and incapable of notable dilatation during the cardiac movements, connect the proximal ventricles which may vary considerably in their strength and in the quantity of blood that they eject, with the distal vessels which are of great elasticity and capable of wide dilatation.

Here, indeed, are most of the specifications one could demand for the construction of a model to illustrate the origin of vascular murmurs—a ventricle which throws more or less blood with more or less force through a fixed ring into a dilating vessel beyond. It is doubtful whether man could construct such a model which would fail to produce a systolic murmur when put into operation.

Why, then, do we not always find systolic murmurs at aortic or pulmonary orifices? This is a question that we cannot answer save by the recognition that nature has so admirably adjusted ventricle, ring and vessel that in normal function, they act as if parts of one elastic tube of constant size.

Palpable and audible vibrations arise, of course, less readily in a viscid medium like blood than in water. But, as a matter of fact, it is just at these points—the aortic and pulmonic orifices—that systolic murmurs are commonest in the normal human being, and of the least significance.

Aortic Orifice. Experimentally¹ in living dogs, murmurs may be caused at the aortic orifice:

- (1) By producing an actual stenosis.
- (2) By bleeding followed by infusion of salt solution, through which the blood is rendered more fluid.
- (3) When conditions are produced in which the excursion of the pulse is greater; that is, in which there is a greater dilatation of the aorta with each systole—as, for instance, in aortic insufficiency.

In the human being such murmurs at the aortic orifice are observed:

- (1) With actual aortic stenoses.
- (2) In dilated and hypertrophied hearts, notably in aortic insufficiency where, with a ring of relatively normal size, a ventricle larger and stronger and with greater capacity, is throwing blood into an aorta capable of wide dilatation.
- (3) With permanent dilatations of the ascending aorta above the ring which are so common either with syphilis or in old age.
- (4) Without obvious cardiac abnormalities, in anæmia—diminished viscosity of the blood—and not infrequently in young neurotic individuals with throbbing vessels—the sort of people in whom loud murmurs are heard in the pulmonary area.

¹ Thayer and MacCallum: AM. JOUR. MED. SCI., 1907, 133, 249.

prob¹ But these are precisely the conditions in which murmurs may be induced experimentally.

In other words, where the ventricle is dilated or hypertrophied or wherever the aorta beyond the ring is relaxed or dilated or wherever the ring itself is narrowed, one may and often does observe a systolic murmur at the aortic orifice.

True stenoses may be recognized by a variety of characteristic phenomena.

Aortic insufficiency, in which systolic murmurs are so very common, is always pathological and easily recognized.

Soft systolic murmurs in the young or in the anæmic, if unassociated with other signs, we have learned fairly well to disregard.

Similar aortic murmurs in men of middle life or past middle life are those which attract our suspicion and demand our attention.

In most cases, with or without evidences of cardiac hypertrophy, such murmurs, in the absence of actual stenoses, will be found to be associated with moderate dilatation of the arch. Dilatation of the arch, often difficult to recognize before the days of roentgenology, is, as is well known, especially common with syphilitic changes which may lead to true aneurysm formation, but it is also exceedingly common with the arterio-sclerosis of age.

These are the murmurs to which I referred a minute ago which are so often ascribed to "roughnesses."

Anyone, however, who is familiar with the pathological anatomy of the aorta must realize that syphilis rarely if ever results in roughnesses which could easily be imagined to set the blood of the entire aorta into audible vibrations; even the extensive calcified plaques of a senile arterio-sclerosis do not, as a rule, give rise to murmurs elsewhere along the course of the vessel.

The cause of these systolic murmurs is the actual or relative dilatation of the ascending aorta above a normally rigid ring. If there be not a true stenosis there is always a relative stenosis depending upon aortic dilatation; this, I venture to assert, is the one adequate explanation of these murmurs.

Murmurs in the Pulmonary Area. The region of the pulmonary artery and conus arteriosus—the second and third left spaces close to the sternum—is the commonest seat of systolic murmurs.

Experimentally, murmurs at the *pulmonary orifice* may be produced in the same way as at the aortic ring:

- (1) By artificial stenosis which may be induced by the very slight pressure of the stethoscope on the thin-walled conus.
- (2) By bleeding and infusion of salt solution.
- (3) When, in the course of the experiment, conditions arise which result in an abrupt cardiac contraction and high pulse pressure in the pulmonary artery.

Clinically, the frequency of murmurs in this area is familiar. They occur:

- (1) With actual stenoses.
- (2) Normally in young individuals, and notably in the neurotic, exaggerated or induced by forced expiration and often disappearing on full inspiration.
- (3) In anæmia.

The pulmonary artery and the conus lie close to the chest wall. In the young with elastic lungs and a large cardiac incisure, the conus may impinge directly upon the chest wall. This impinging during systole against the chest wall should reproduce exactly the conditions which exist experimentally when one presses a stethoscope against the conus.

With a deep inspiration, however, a soft cushion of lung is interposed between ventricle and chest; under these circumstances the murmur disappears.

Auriculo-ventricular Orifices. If it be true that with normal cardiac function the ventricle, the arterial orifice—constriction through it may appear—and the vessel beyond so comport themselves as to represent a single tube, the same is true of auricle, atrio-ventricular orifice and ventricle in diastole.

The tricuspid and mitral rings in normal function behave not as straits, but as parts of a common auriculo-ventricular canal. Only with actual stenoses of these orifices do audible or palpable vibrations arise when the blood is flowing in its normal course.

Apical Systolic Murmurs. But, as is familiar, systolic murmurs may arise at the auriculo-ventricular orifices.

Experimentally, apical systolic murmurs may be produced in the dog by incision or laceration of the mitral valve. This, as one might expect, results in:

- (1) Palpable and audible vibrations arising at the opening through which the regurgitant current passes backward into the auricle; the opening is a point of constriction in the course of the regurgitant blood. The thrill and murmur at this point are usually of great intensity. But the auricular wall adjacent to the mitral valves cannot be reached even in the widely open dog's chest, save by awkward manœuvres. As the heart lies in position one cannot reach the auricle; one can place the stethoscope directly over the left ventricle only at the apex of the heart. But this point, lying proximally to the seat of origin of the vibrations, is, physically, a relatively unfavorable spot for the transmission of the sound. In experimental mitral insufficiency the thrill, so easily palpable on the auricular side of the valves, is lost at the apex where the murmur, instead of being harsh and rasping, becomes soft and blowing, like the systolic murmur of mitral insufficiency as heard in the human being.

prob' (2) Like murmurs arise without valvular damage on the
 W development of dilatations of the mitral ring which may be brought about by overdistending the heart or as a result of failure of the muscles toward the end of the experiment.

Experimentally, then, in the dog, systolic murmurs heard best in the region of the apex and similar to those heard in mitral insufficiency in the human being, may be produced by damage to the mitral valve or by dilatation of the auriculo-ventricular orifice.

Clinically, in the human being, a systolic murmur heard in the region of the apex is a common phenomenon.

Such murmurs are observed:

- (1) In disease of the valves resulting in insufficiency.
- (2) In muscular weakness resulting in dilatation of the mitral ring, which is observed under a variety of conditions.
- (3) Normally, as so-called functional murmurs, the commonest varieties of which are
 - (a) Apical systolic murmurs in normal young individuals heard in the recumbent and left lateral posture.
 - (b) Cardio-respiratory systolic murmurs.

Apical systolic murmurs are not generally of very great intensity for the obvious reason that the points at which we are able to approach the heart with our stethoscopes are situated proximally to the point of origin of the murmur. They are commonly heard in axilla and back because, even though considerable lung be interposed between heart and chest wall, the root of the left ventricle and the left auricle over which the murmur is of greatest intensity, lie posteriorly.

It is well to remember in connection with indirect mitral murmurs, as with direct aortic murmurs, that the cause of the murmur is the passage of blood through a narrow orifice into a wider chamber, and not, as a rule, the result of interference with the current by vegetations or roughnesses at the orifice itself, save in the case of large calcified masses. It is not likely that vegetations in themselves play any essential part in producing audible vibrations save, perhaps, the large thrombotic vegetations of a bacterial endocarditis.

The assumption that the systolic murmur of mitral insufficiency is usually due to roughnesses and vegetations on the valves, even in acute rheumatic endocarditis, is very common. One has, however, but to reflect on the character of the lesions of acute rheumatic endocarditis to realize that the tiny verrucosities along the line of meeting of the valves would be quite incapable, of themselves, of producing sonorous vibrations. The early murmurs arising at the mitral orifice in acute rheumatic heart disease are not due to the endocarditis but to the relaxation of the mitral ring due to myocardial change. It is only with the subsequent chronic thick-

enings and curlings of the valve curtains and shortening of ^{were} chordæ tendineæ, that recognizable insufficiencies and stenoses occur. This is why all cases of acute rheumatic fever should be kept under observation for weeks or months after recovery from the acute symptoms. - In many such cases the appearance of chronic valvular disease gives evidence of a previously unrecognized acute change;² in others the disappearance of the murmur proves its myocardial origin.

But how about those obvious insufficiencies with grave cardiac failure that may occur relatively early in an attack of acute rheumatism? Are we wrong in assuming that these indicate the existence of an endocarditis?

Yes and no.

We are *wrong* in the sense that an acute rheumatic endocarditis could not of itself produce such signs and, as a matter of fact, has nothing to do with them. *But acute rheumatic heart disease is, in almost all cases a pancarditis*, and the early cardiac dilatation which results in the systolic murmur is dependent upon the acute myocarditis.

We are *right* in assuming that these signs are suggestive of an acute endocarditis because, in the great majority of cases, endocarditis accompanies the myocardial and pericardial changes.

1. *That a given apical systolic murmur may depend upon actual valvular disease* is suggested by:

- (a) The history of previous conditions commonly associated with endocarditis — rheumatism, chorea, repeated tonsillitis.
- (b) Evidences of an associated bacterial endocarditis.
- (c) The coincidence of signs of mitral stenosis.
- (d) The presence of a murmur of a specially harsh and rasping character.

2. *That such murmurs depend upon dilatation of the mitral ring* may be suggested by:

- (a) The absence of a history pointing to preëxisting valvular disease.
- (b) Their development in the course of progressive hypertrophy and dilatation from hypertension or syphilitic aortic insufficiency.
- (c) Their appearance in the course of acute infectious fevers not commonly associated with endocarditis or in grave anæmias with great muscular weakness.
- (d) Acute heart failure occurring in the early stages of rheumatic heart disease.

3. *That the murmurs are functional* and of no pathological significance may be suspected:

² Thayer: Jour. Am. Med. Assn., 1906, 47, 1352.

prob¹
W (a) *In young people under thirty years of age, especially in women but often in boys when the patient is examined in the recumbent posture and when the murmur is accompanied by a louder murmur in the pulmonary area. Under these circumstances systolic apical murmurs are very common. The heart sounds are generally of a normal character but the first sound at the apex is followed by a fairly distinct whiff which may or may not be transmitted into the axilla. The murmur is usually increased when the patient lies in the left lateral posture. These murmurs are generally heard all over the heart and loudest in the pulmonary area; but sometimes they are loudest at the apex, and sometimes they are not heard at the base. In the erect posture, the murmur disappears at the apex and diminishes in intensity if it does not disappear at the base on full inspiration. Sometimes it disappears at the apex on full inspiration suggesting that it is a transmission of the basic sound.*

Such murmurs are extremely common and of no pathological significance.

During my studies of the third heart sound some years ago, among 218 apparently healthy individuals in the first four decades of life, 74 or over one-third showed systolic murmurs at the apex in the recumbent posture.

FREQUENCY OF SYSTOLIC MURMURS AT THE APEX OF THE HEART IN
OTHERWISE NORMAL INDIVIDUALS IN THE RECUMBENT
POSTURE.

Decades	1*	2	3	4
Cases	39	98	55	26
Murmurs present	22	35	12	5
Percentages	56.4	35.7	21.8	19.2

Among 30 healthy school boys in the second decade of life, 18 (60 per cent), showed systolic cardiac murmurs. In all, the murmur was heard in the pulmonic area; in 13 (43.3 per cent), it was audible at the apex as well as in the recumbent or left lateral posture. In the erect posture the heart sounds were clear at the apex.

I am inclined to think that in most instances, the systolic murmur heard at the apex in the recumbent and left lateral posture is but a transmission of the basic sound although it has, in my mind, always been a question whether posture may not, sometimes, cause a true functional mitral insufficiency.

(b) *In the case of cardio-respiratory murmurs, with the abrupt emptying of the ventricles in systole the place*

* None under three years.

occupied by the full ventricle is compensated for³ by a slight collapse of the overlying chest and an accentuated rush of air into the overlying lung. This brings it about that, with each systole, there is, often, a rhythmical accentuation of the inspiratory murmur and sometimes even a slight sound during expiration. This sound may be extraordinarily like the murmurs depending on an actual mitral valvular insufficiency. That it should be similar in character has been explained by studies in Mueller's³ Clinic which show that the physical characteristics (the dominating tones of the ordinary inspiratory murmurs) are very close to those of the common systolic murmurs of mitral insufficiency.

Cardio-respiratory murmurs are sometimes heard with greatest intensity toward the base, more often, in my experience, toward the apex of the heart. They are always accentuated during inspiration, and usually disappear at some stage of respiration, generally when a full breath is held. They are always recognizable to the careful student, but if one does not pay careful attention, they may be very misleading. This is especially true since it is not generally appreciated *that these murmurs may be heard with greatest intensity in the back over the left lung*, notably in young individuals with throbbing hearts. I have seen more than one false diagnosis of organic heart disease made in such cases where a little careful attention would have made the nature of the murmur perfectly clear.

Systolic murmurs arising at the tricuspid orifice I shall not discuss.

Summary. I have tried especially to emphasize several simple points:

1. That it is not the frequency of soft systolic murmurs at aortic and pulmonary orifices that is remarkable. What is remarkable is that they are not always present.*
2. The presence of such murmurs depends upon the relative stenosis represented by the more or less rigid aortic or pulmonary ring and the dilatability or dilatation of the vessel beyond. The frequency of such murmurs at the aortic orifice in later life is, in the majority of instances, dependent upon a greater or less dilatation of the arch, not upon roughnesses at the aortic ring.
3. The frequency of functional systolic apical murmurs in the young when in the recumbent posture.
4. The importance of recognizing cardio-respiratory murmurs and the realization that they are often heard with considerable intensity in the back.

³ Lancet, London, 1913, 1, 674.

* This remark is not original. It has been made, I think, by Broadbent.

prob¹

W STUDIES IN HUMAN CONSTITUTION: FACIAL FORM AND DISEASE CORRELATION.

BY GEORGE DRAPER, M.D., HALBERT L. DUNN, M.D.,

AND

DAVID SEEGAL, M.D.

(From the Department of Medicine of the Columbia University, College of Physicians and Surgeons and the Presbyterian Hospital.)

THERE is no doubt in any one's mind that, for him who has learned to read it, the face of Man is an open book. Indeed clinicians have placed such great value upon the facial expression of sick people that in some instances, as for example the "Hippocratic facies," a diagnosis is based upon it. In Dorland's medical dictionary there are thirty-two different disease facies described. But like much of the information which free observation brings to the physician, it is often difficult for him to define just what it is that he has seen. Strangely enough too, the most carefully trained doctors, in respect to correlations between facial aspect and disease, have used essentially the arts of the physiognomists and phrenologists. These supposedly fanciful observers, however, who have sought to make correlations between psychic pattern and facial form, have at least attempted to base their anatomical data upon definite measurement. John Hunter,¹ Blumenbaeh,² Cuvier³ and Petrus Camper⁴ all studied the comparative relationships of face and head size. The work of these observers was stimulated partly through interest in the different races of mankind and partly by a desire to correlate with facial form the psychological, emotional and temperamental differences between races and individuals. Darwin⁵ made many observations upon facial expression. Still later Laycock⁶ wrote extensively on "Physiognomical Diagnosis."

In connection with the general study of human constitution, which is in progress at the Presbyterian Hospital, our attention has been drawn to certain measurable recurring facial characteristics. In this study of constitution, as was pointed out in a previous paper,⁷ all patients have been divided into groups according to the disease from which they suffer. In the present report inter-disease group comparisons have been made between the anatomical facial differences of 5 disease types, namely, people having gall bladder disease, gastric and duodenal ulcer, nephritis hypertension, pernicious anemia or tuberculosis.

The material upon which the study is based consists of 280 cases: 161 males and 119 females. Seventeen of the 161 male patients belong to the gall bladder group, 21 to the pernicious anemia, 18 to the nephritis hypertension, 30 to the gastric and duodenal ulcer

and 75 to the tuberculosis. Thirty-three of the 119 females were gall bladder patients, 23 pernicious anemia, 20 nephritis hypertension, 15 gastric and duodenal ulcer and 28 tuberculosis.

In analyzing the variation between human faces it is necessary first to define what constitutes the face (Fig. 1). The usual conception of the face is a perpendicular oval bounded superiorly by the hair line. Anthropometrically, however, the face is limited superiorly by a horizontal line drawn through the nasion. In this more restricted sense, the face is a more or less squat horizontal truncated oval; the facial diameter being always of greater length than the facial height.

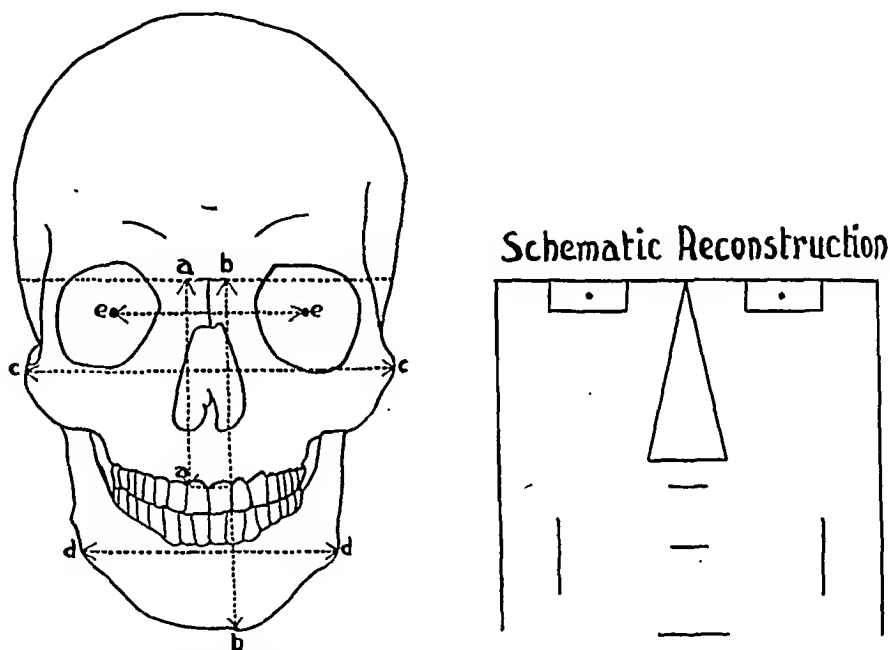


FIG. 1.—Facial measurements. aa, nasion prosthion (upper facial height); bb, facial height; cc, facial diameter; dd, gonial diameter; ee, interpupillary space.

The facial measurements which have been used are 10 in number: (1) Nasion prosthion (aa, Fig. 1), from the nasion to the maxillary alveolar point; (2) the facial height (bb, Fig. 1), from the nasion to the menton (mental tubercle); (3) facial diameter (cc, Fig. 1), the widest interval between the zygomatic arches; (4) bigonial diameter (dd, Fig. 1) or distance between the angles of the mandible; (5) interpupillary space (ee, Fig. 1) taken to the center point of each pupil; (6) infradental menton, distance from the mandibular alveolar point to the mental tubercle; (7) nasal height, from the nasion to the lower border of the nose, where it meets the lip; (8) nasal breadth, distance between the outer surface of the alæ nasæ; (9) palpebral length or length of the eye slit and (10) palpebral breadth, the greatest distance between the upper and lower lids with the eye fixed on a distant object.

The schematic reconstruction of these measurements, as shown in Fig. 1, illustrates the inadequacy of anthropometrical determinations for reproducing what is seen by the human eye.

Obviously the good clinician sees much more in the face of his patient than can be measured by instruments. That which he observes is a summation of three distinct elements:

The element which the eye catches first and most readily is that produced by the distribution of the soft parts and by the muscles of expression. The scope of this paper however, cannot include a discussion of expression, a subject which has been dealt with at great length by scientists, philosophers, and artists. But it is important to remember that almost every degree of form and expression may clothe the same bony framework. Emotional influences, physical conditions, malnutrition or endocrine disturbances may change the expression of the same individual beyond recognition.

The second element is the strong impression produced solely by differences in actual size. To demonstrate this effect we have compared the average facial measurements of 21 pernicious anemia males with those of 9 acromegalics. The pernicious anemia and acromegalic faces were reconstructed schematically as shown in Fig. 1 and the angle of the jaw was arbitrarily fixed in order to complete the facial outline. It is evident (Fig. 2) at once that the acromegalic features are very much larger than those of pernicious anemia people. When the pernicious anemia features are raised proportionately to the same scale as the acromegalic, however, they prove to be practically identical.

The third element is the effect of relative size or in other words true proportional differences. This third element will now be discussed in detail.

The study of relative differences has been made by intercomparison of the bony measurements and the interpupillary space. These have been related to one another as indices.

Three indices have been used and are shown in Fig. 1:

The first or facial index is formed by dividing the facial height by the facial diameter and multiplying by 100. It expresses facial height in per cent of facial diameter. It is an index of the relative breadth or length of the face as a whole. Consequently a low index means a wide, short face.

The second or upper facial index is formed by dividing the nasion prosthion length by the facial diameter and multiplying by 100. It expresses the relative width of the upper facial zone, or that region which lies between the nasion and the mandible. A diminishing index here signifies a wide, short upper facial zone.

The third index expresses the relative proportions of the eye-nose zone. It is formed by dividing the interpupillary space by the nasion prosthion and multiplying by 100. It is important to observe that

unlike the two preceding indices this one is formed by dividing a breadth by a vertical measurement. As the index becomes smaller the nasion prosthion grows larger and, therefore, a small index signifies a narrow eye-nose zone.

The relative differences between disease groups are proven by indices and by arithmetic averages. The graphs, Figs. 3 and 4,

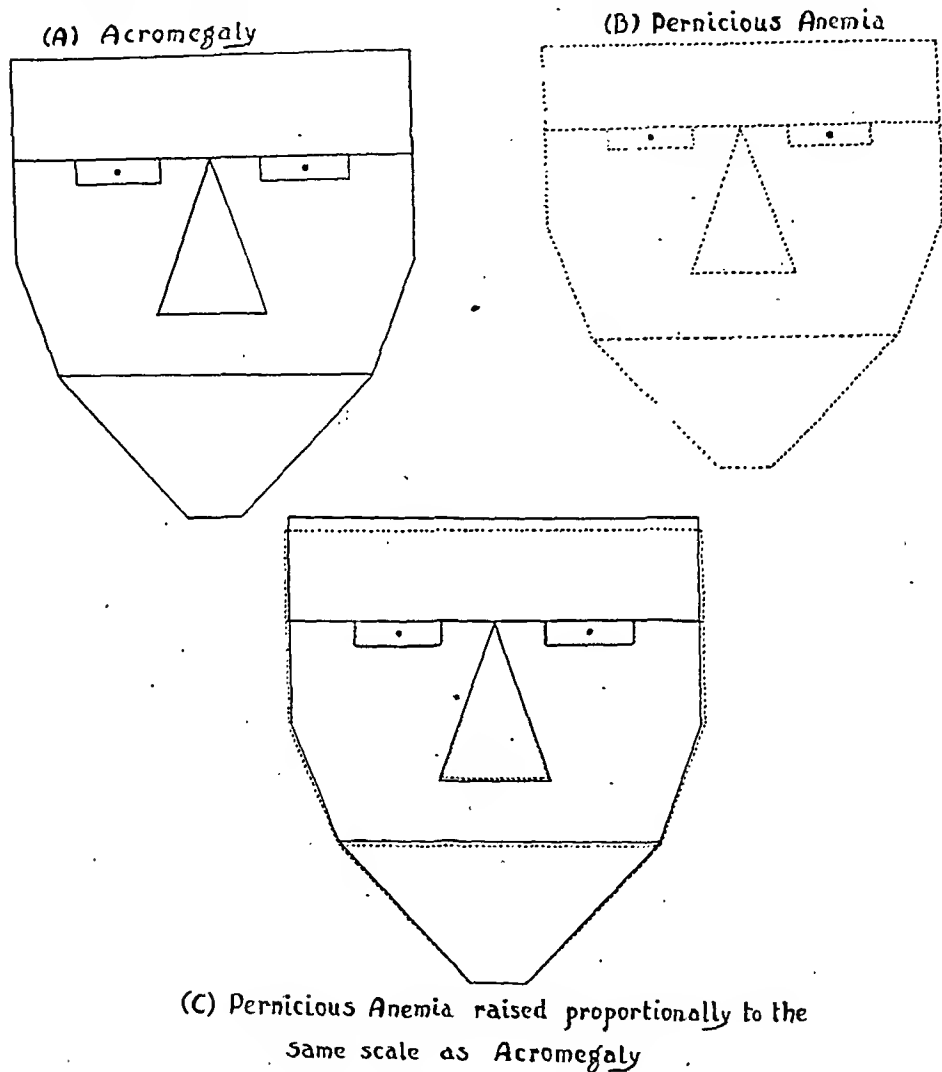


FIG. 2.—Actual and relative comparison of face size and shape. *A* and *B*, actual size; *C*, relative size.

are accumulative percentage frequency curves, the ordinates of which represent the per cent of total number of cases and the abscissæ the value of the respective index. These curves are of primary value in showing the distribution of individual cases. The table is based on arithmetic averages of the data. Three measurements are recorded in per cent of facial height and the interpupillary space is also given in per cent of the facial width.

The anatomical facial differences between the 5 disease groups (Figs. 3 and 4) may be summarized as follows:

In all disease groups the face of the male is consistently more narrow in proportion to its height than is that of the female.

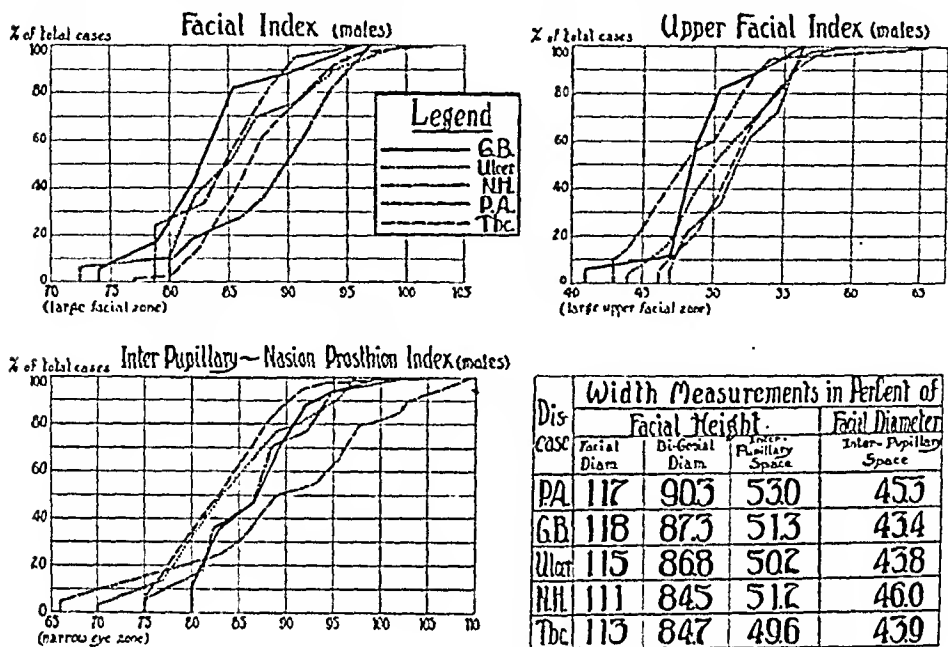


FIG. 3.—Facial differences in males in five disease groups.

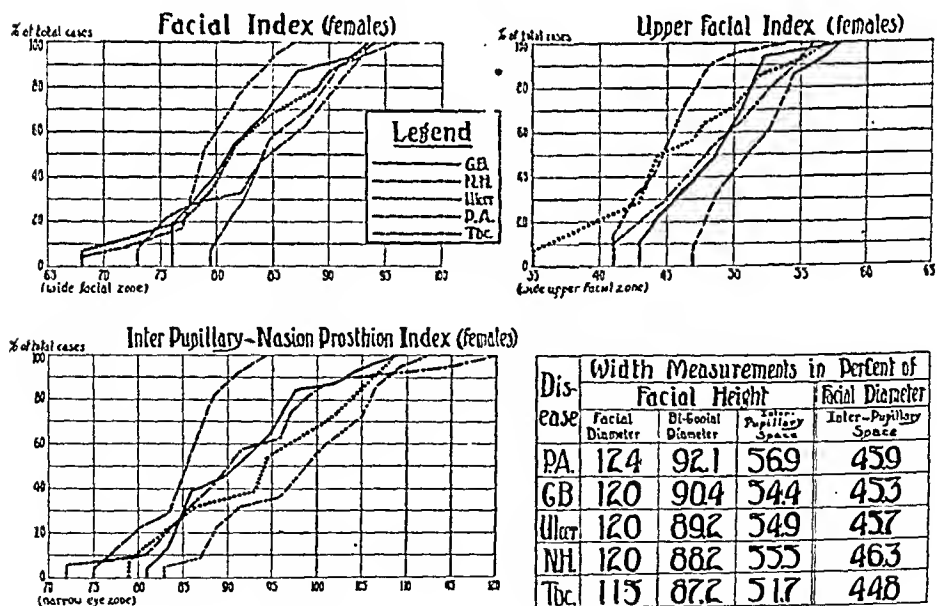


FIG. 4.—Facial differences in females in five disease groups.

Gall bladder and pernicious anemia people have wide faces and wide upper faces. The female faces of the pernicious anemia individuals are considerably wider than those of the gall bladder people.

Pernicious anemia people have wider lower faces than do the gall-bladder as shown by the relatively large bigonial diameter for both male and female. They also have much wider eye zones than the gall bladder people as demonstrated by the interpupillary-nasion prosthion index. Nephritis hypertension people and tuberculosis

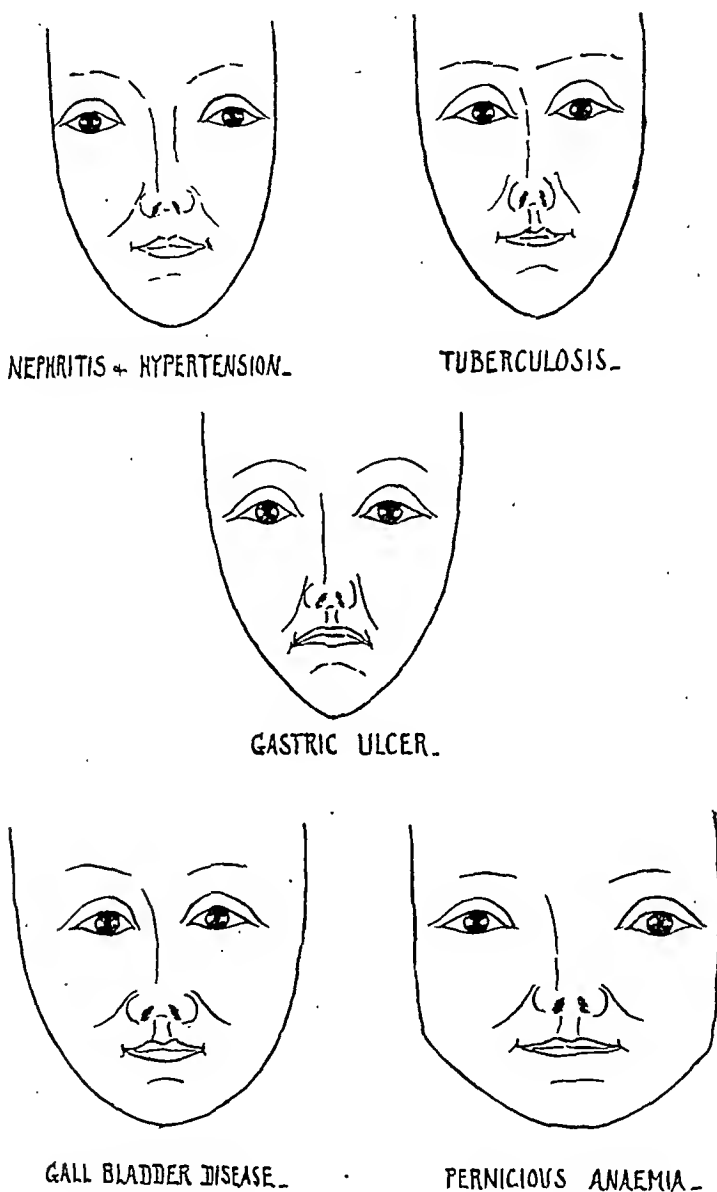


FIG. 5.—Semischematic faces, emphasizing basic proportional differences.

individuals, on the other hand, have relatively narrow faces. The nephritis hypertension group has comparatively broad eye zones in contrast with the tuberculosis type which has very narrow ones. Ulcer people are intermediate in all respects. The accumulative percentage distribution curves check with the results based on the arithmetic averages. When the interpupillary space is expressed

in per cent of the faecal width, the nephritis hypertension of both sexes appear to be particularly wide-eyed because of their narrow faces. The gall bladder individuals, on the other hand, have narrow set eyes in respect to the width of their faces.

The principal differences between the faces of various disease types (Fig. 5) are shown by exaggerated sketches based on these mathematically proven variations: (1) the long, thin nephritis hypertension face with its wide set eyes; (2) the equally long, thin tuberculosis face with its narrow set eyes; (3) the wide rounded gall-bladder countenance with its relatively narrow eyes; (4) the wide pernicious anemia features with its very great interpupillary space and its wide jaw angles; and finally, the ulcer face which is intermediate in every respect.

Summary. 1. There are differences both actual and relative in the bony skeleton of the face and the eye placement of different disease races.

2. The good clinician can observe differences between the faces of his patients by analyzing separately the effect of soft parts and expression, the effect of actual size, and the effect of relative differences in the faecal indices and the eye placement.

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CONGENITAL FIXATION OF THE DUODENUM.

BY WALTER L. NILES, M.D.,

NEW YORK.

THE frequent occurrence of adhesions or bands within the peritoneal cavity has long been recognized by pathologists and anatomists, Virchow,¹ in 1853, having published a comprehensive and instructive article on the subject. They were formerly regarded as inflammatory in origin but evidence has accumulated which shows quite conclusively that in fetal and early life, at least, they are congenital, and that most of those occurring in later life are likewise due to developmental defects.

Important observations have been recorded by Morris,² Robinson,³ Opitz,⁴ and others; but by far the most valuable have recently been published by Bryant⁵ whose painstaking observations and analyses form a basis for the most accurate data now available. He concludes that the frequency of occurrence of peritoneal bands has been greatly underestimated, as he found them present in 91.1 per cent of his male cases, which included 18 fetuses, and in 85.5 per cent of the female cases, which included 16 fetuses.

Convincing evidence regarding the developmental origin of such bands is also found in Bryant's observation that until the age of forty there is no material increase in the frequency of peritoneal bands above the percentage of involvement found in fetuses. Furthermore, he observed that the bands which are found with the greatest frequency in adults are the ones most frequently found in fetuses. The developmental or congenital origin of these folds, or membranes, or adhesions, can, therefore no longer be doubted.

The types of bands found and their frequency in both sexes as reported by Bryant is shown in the following table:

	Male, per cent.	Female, per cent.
Gall bladder to the duodenum and the transverse colon	25.6	24.8
Gall bladder to the transverse colon	17.2	9.4
Gall bladder to the duodenum	15.5	17.9
Appendix to the peritoneum	15.0	5.9
Omentum to the ascending and the transverse colon .	11.1	12.0
Ascending colon to the transverse colon	10.6	5.9
Duodenum to the peritoneum	6.7	10.3

A study of this table shows that in both sexes the bands which have their origin around the gall bladder comprise a majority of all the bands which were observed, namely, 57.3 per cent in the male cases and 59.7 per cent in the female cases. Harvey (reported by Homans) studied the frequency of bands running from the gall-bladder to the duodenum in infants and found them present in 19 per cent of his cases, a figure which compares with Bryant's very closely.

It appears evident, therefore, that the frequency of congenital bands in the abdomen has heretofore not been appreciated and my observations lead to the conclusion that their clinical significance is of greater importance than is generally realized. Several types of bands are often found in the same individual as shown by Bryant's table of frequency mentioned above, and any or all of them may play a part in producing symptoms. I shall, however, confine my remarks to the most frequent type, which also, I believe, causes the most severe and definite symptoms, namely, those which have their origin about the gall bladder and pass to the duodenum alone, or to the duodenum and the transverse colon.

The first to appreciate the clinical significance of the hepato-duodenal type of band, so far as I know, was M. L. Harris,⁶ who in

1914 reported a group of 6 cases on whom he had operated upon with uniformly gratifying results, and in our clinic we have come to refer to them as "Harris' Bands." Since the publication of Harris' paper, 2 other series have been reported, 1 by Homans,⁷ who in 1916 reported 17 operated cases, and in 1917 Hill⁸ reported 4 operated cases. Although I recognized several cases soon after reading Harris' report, I was then inclined to regard it as a rather rare condition and relatively unimportant; but further observations have convinced me that it is frequently the cause of distressing symptoms and I believe that a considerable percentage of the illy-defined, chronic disturbances of the gastrointestinal tract which are variously diagnosed as chronic colitis, auto-intoxication, enterostasis, periduodenal adhesions, and so forth, have their origin in this kind of lesion. During the past ten years, 39 of my patients have been operated upon for this condition and their records form the basis for my report. I have also seen about 150 others in whom the diagnosis was made but who for various reasons have not been operated upon.

Of my 39 cases operated upon, 31 (80 per cent) have been females and 8 (20 per cent) males. The greatest number, 15, have been in the third decade when operated upon. The youngest was fifteen years of age, the eldest 67. The duration of symptoms varied from six months to twenty years, the average being about twelve years. In general the older the patient the longer the complaint of symptoms.

A review of the histories shows that in almost all instances digestive disturbances existed in infancy and childhood. Some were difficult babies to feed, some had eczema, several were reported to have had "cyclic vomiting" or acidosis. Some vomited when fatigued, or emotionally upset; others had "bilious attacks" and headaches; three had epilepsy and practically all always had been constipated.

So far as symptoms are concerned, the cases may be divided into two classes, (a) those characterized by attacks of epigastric pain, and (b) those which are toxic and complain of indigestion, usually not painful. It is impossible to sharply separate these classes for those in which paroxysms of pain predominate always show some evidence of intoxication and the toxic cases usually, though not always, have some epigastric pain at times.

The painful cases are less numerous than the toxic, 12 (30 per cent) having been so classified. A typical example is that of a woman, aged thirty-four years, who always had been constipated but generally well. One morning, seven years ago, she arose feeling perfectly well and went to business as usual. About two hours after a hearty luncheon she began to have pain in her epigastrium. It was not agonizing but compelled her to go home and kept her awake all night, subsiding the next morning when her bowels moved.

It was felt chiefly beneath the ribs on the right side of the epigastrium and did not radiate. It varied in intensity from time to time but there was no cessation at any time. She belched gas but was not nauseated and did not vomit. During the next four years she suffered with recurring attacks of a similar nature at irregular intervals, varying from three to seven weeks. Her appendix was removed three years ago and a tonsillectomy was performed last year. However, the pain has increased in severity and before operation was present practically all of the time, so that her sleep had been seriously disturbed. Large meals, coarse food, fatigue and emotional upsets were thought to precipitate painful attacks. Such cases gradually develop more and more of the symptoms described with the toxic cases.

The second or toxic group present the general picture which we all recognize as neurasthenia with indigestion, especially characterized by flatulence. Chief among these manifestations are fatigability, nervousness, palpitation, tachycardia sometimes, headache often, occasionally migraine, insomnia and mental depression. These symptoms frequently overshadow the gastric picture.

The gastrointestinal symptoms may be described as follows: From one-half to two hours after meals a sensation of weight or fulness or oppression is felt in the pit of the stomach. This is referred to as gas and if belching can be induced some relief follows. Many take bicarbonate of soda for this purpose and some find relief by an enema. Headache, nausea, nervousness and depression often accompany this indigestion. There is no distress when the stomach is empty and those who take little for breakfast may have no discomfort until after lunch. Large meals and coarse food cause more distress. Most of these patients have actual pain occasionally, but it is not very severe. Nausea is frequent and in some is almost constant. Most patients vomit occasionally, especially after physical exertion or mental fatigue. Blood is never vomited. Heartburn and pyrosis are only occasionally noted. Moderate loss of weight is usual and in some becomes considerable.

Constipation is the rule and it is often severe, most cases having always been constipated. This is sometimes relieved by attacks of diarrhea, and mucous colitis was noted in six cases. Examination of the stools reveals nothing characteristic. Mucus is usually in excess but blood is not found. Carbohydrate fermentation is more frequent than protein putrefaction, though either may occur. The bacterial flora may be changed accordingly but has no diagnostic significance.

The gastric contents are not characteristic though very marked hyperchlorhydria has been found in a few instances. A moderate degree of secondary anemia is usual and in a few cases the anemia has been severe.

Physical examination reveals a flabby, nervous patient with sallow

skin and poor muscle tone. The reflexes are oversensitive and vasomotor irritability is evident. Palpation of the abdomen usually, but not invariably, elicits tenderness just to the right of the median line and about midway between the costal margin and the umbilicus. In some the pressure of clothing is quite uncomfortable. The cecum is usually distended and sometimes thickened and tender, the result of back-pressure from spastic contraction of the sigmoid colon or, as I shall subsequently describe, it may result from accompanying bands in the ileocecal region or ascending colon.

While abnormal fixation of the duodenum should be suspected from the symptoms above described, the diagnosis chiefly depends upon roentgenological examinations with an opaque meal. Observations with the fluoroscopic screen are more satisfactory and elicit more direct evidence than do films, but both methods should be utilized. To be certain of the degree of movability of the duodenum by films only, it is necessary to make a considerable number of exposures with the patient in various positions.

Upon roentgen-ray examination a fish-hook type of stomach is usually found. The steer-horn type is occasionally observed and it is difficult to demonstrate fixation of the duodenum in such cases. There is accumulating evidence which suggests that all such stomachs are accompanied by and due to peritoneal bands, but I am not yet certain of it. The pyloric end of the greater curvature frequently presents a prognathian contour and this is very suggestive of duodenal fixation. The pylorus is found distinctly further to the right than normal and very high, generally opposite the first or second lumbar vertebra. The duodenal cap often fills slowly, apparently because of spasm, and when filled is usually dilated. The first portion of the duodenum is also moderately dilated and it characteristically passes to the left and upward. The so-called hepatic flexure of the duodenum at the junction of the first and second portions is also very high, just under the liver, and its upper margin and the descending limb of the duodenum are often flattened by pressure against the liver. The apex of the duodenum is firmly held in a position which allows no lateral movement and little or no up and down displacement, except with respiration. The sharp angulation in such cases gives the appearance of a soft tube suspended on a hook. Passage of the opaque meal is often delayed at the apex of the duodenum but it passes on in a normal manner after a few minutes. In other cases the duodenum represents three sides of a square with the upper portion lying quite horizontal, held up against the liver, flattened and firmly fixed.

While there is always some obstruction at the point of fixation, it is relatively slight. The stomach almost always empties on time and in only three of my cases was there definite gastric dilation. The tone of the peristaltic waves is good and in a few instances there

has been hyperperistalsis; such cases have at operation showed hypertrophy of the musculature.

The condition is very frequently overlooked by roentgenologists, usually because they are not familiar with it and therefore do not look for it. Some do not use the fluoroscopic screen enough and also make too few films to demonstrate it clearly. The points which I have mentioned must be kept in mind and searched for. It is also important to make observations with the patient in various positions and with varying degrees of pressure upon the epigastrium by the hand or by air cushions. By careful study an accurate diagnosis can be made in a very high percentage of cases.

The conditions for which hepatoduodenal bands are usually mistaken are cholecystitis with adhesions to the duodenum, duodenal ulcer or chronic appendicitis. Two-thirds of my surgical cases had previously had an appendectomy. If the gastric symptoms are not very severe, they have been considered neurasthenic or diagnosed chronic colitis with intestinal intoxication. In the painful cases attention is naturally centered upon the gall-bladder. The pain is, however, never so severe as that of biliary colic, seldom requiring the use of morphin, and the early age at which symptoms usually begin, together with the roentgen-ray findings, serve to differentiate. Periods of remission are frequently noted early in the history, but the symptoms eventually become quite continuous and lack the periodicity and hunger-pains that characterize peptic ulcer. Blood is not found.

While it is obvious that surgery offers the only means for removal of this condition, I wish to emphasize the fact that it is by no means necessary to operate upon all cases in order to relieve the symptoms. In my experience fully half of them can be more or less permanently relieved by medical means. It is a difficult problem to decide which patients shall be operated upon and a decision must be based upon numerous factors. Fortunately the condition is not in itself lethal nor are the effects rapidly progressive, so that one is justified in exhausting medical measures before advising an operation. The following points should in any case be considered: (a) The degree and extent of the duodenal fixation; (b) evidences of back-pressure; (c) severity of the symptoms, including the state of the nervous system; (d) the age of the patient; (e) whether proper medical treatment has been instituted and its effect; (f) the type of case, whether painful or toxic. If the patient has suffered for many years, becoming more and more incapacitated, and, as in many instances, has been on a rational regime for months or years without relief, then operation should be undertaken at once; also those cases which suffer with frequent, or more or less constant, pain and in whom the roentgen-ray evidences are marked, particularly with signs of back-pressure, should be operated upon. Mild cases, especially the toxic ones, with no delay in the passage of barium, little impairment of

strength and nutrition and with stable nervous systems, should be given a trial with medical treatment. If the response is not prompt and improvement easily maintained, they should then be operated upon, for otherwise they will almost certainly gradually decline in health and efficiency. I am more inclined to advise operation in the young patients of twenty years or so than in those at middle life, for the reason that they make a very prompt and permanent recovery, and I believe that if the condition remains unrelieved they are prone to lapse into chronic semi-invalidism as the increasing stress of life tends to aggravate the digestive and nervous systems. It is, however, difficult to estimate what the effects may be after a period of years and this I think depends a great deal upon the inherent quality of the nervous system. If the heredity is good and the nervous system stable, one is justified in longer delay than when the opposite picture is presented. When the nervous system is seriously deranged, it is better to proceed with the operation immediately, rather than to attempt to improve the general condition before operating, for I believe that in such cases the duodenal lesion is the exciting cause for the nervous derangement.

Medical treatment is often highly satisfactory. It consists in giving a diet which is non-irritating in both its chemical and mechanical constituents. All foods should be thoroughly cooked, finely divided and simply prepared and they should be given in small quantities and at frequent intervals. After the heavier meals at least, patients should lie down for an hour with the hips elevated. Due regard should be given to disturbances in gastric secretion. Many of the symptoms are due to pylorospasm as well as spasm of the duodenum itself and relief is often obtained by a mixture of belladonna and a bromide administered before meals or by benzyl benzoate given after meals. These are also useful in overcoming spasm of the sigmoid colon, which is quite constantly an accompaniment of spasms elsewhere and which is the usual cause of the constipation. A most important and fundamental point in treatment is to restore the tone of the supporting muscles and to elevate the stomach in order to relieve traction upon the point of duodenal fixation. This is accomplished by wearing an abdominal belt when in the upright position and by exercise, massage, etc., to restore the muscles in question. The operative procedure consists in simply dividing the band which, by releasing the duodenum, allows it to assume its normal position and contour. It is of course very important to suture carefully all cut and torn peritoneal surfaces, in order to limit the formation of adhesions as much as possible. Some surgeons place a layer of rubber tissue between the cut surface, leaving it in for two or three days to prevent adhesions. A transverse right rectus incision is advocated by Alfred S. Taylor who has operated on some two hundred cases. It gives ready access to the pyloric region and also to the right iliac fossa and if adhesions follow,

as is always probable, they will perhaps be in a more favorable position than when a vertical incision is made. About ten days after operation massage of the abdomen should be commenced to mobilize possible adhesions and improve the tone of the abdominal and intestinal muscles. A bland, low-residue diet is ordered for about three months, after which a coarse diet may be substituted. Constipation is invariably lessened, and often entirely relieved within a few weeks.

My experience in these cases again emphasizes the importance of exploring every abdomen which is the seat of chronic disease, whenever it may be opened; observance of this rule would obviate many subsequent operations. I have come to regard a previous appendectomy as a typical feature of this group of cases and it has almost invariably been done for so-called "chronic appendicitis." Twenty-eight of my 39 operated cases had had their appendices removed previously. Reference to Bryant's statistics shows that 40 per cent have other peritoneal bands, most of them in the right side of the abdomen; these should of course be sought for and relieved when operating. Although associated with a hepatoduodenal band, they may be chiefly responsible for the symptoms and in some cases it is impossible to conclude which band has been of most importance. In any event they should all be relieved as far as possible. I have no doubt that in some of my cases pericolic membranes have played a large part in the symptomatology.

The results of operation have been exceedingly satisfactory and I know of no abdominal condition which offers a greater assurance of relief by surgery. Those patients who suffered attacks of pain or painful distress in the epigastrium have been absolutely, and usually immediately, relieved. Symptoms referable to the stomach have generally ceased; they are always much improved. Constipation has invariably been helped and frequently cured. Vasomotor instabilities and the so-called neurasthenic symptoms have always improved, though a longer period is naturally required than to secure relief from the digestive symptoms. It is a very striking fact that the shorter the history of well-marked symptoms, the more perfect and more immediate the cure. Every one of my patients whose history was less than five years in duration is in perfect health. This group is chiefly, though not wholly, composed of young patients and it offers another reason for operating more freely and sooner in the young than in the middle-aged or old people. It is very difficult to foretell how complete will be the relief in any given case, and I have been amazed at the remarkable improvement which has followed operation in some of my older patients. It is, however, true that the least satisfactory results have invariably been in patients over forty years of age.

The maximum results from operation often do not occur for at least one, and sometimes for two years, and it is exceedingly impor-

tant to keep patients under treatment, which is chiefly dietetic and gymnastic, until they are cured.

Summary. 1. Congenital bands in the abdomen are much more frequent and of greater clinical importance than is generally recognized.

2. A study of 39 cases of the hepatoduodenal type, which came to operation is reported.

3. While fully half of this type of cases can be more or less permanently relieved by medical means, the results of operation have been exceedingly satisfactory. Surgery should undoubtedly be utilized in selected cases.

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OBSERVATIONS ON THE HEMOHISTIOBLAST OF FERRATA.

BY MAURICE N. RICHTER, M.D.,

INSTRUCTOR IN MEDICINE, COLUMBIA UNIVERSITY, COLLEGE OF PHYSICIANS AND SURGEONS; PATHOLOGIST TO THE FIRST MEDICAL DIVISION, BELLEVUE HOSPITAL, NEW YORK.

IN the course of certain pathological processes a growing literature attests that latent potentialities of the connective tissues may become manifest by their differentiation into various types of blood cells, as granular and non-granular leukocytes.*

Important evidence in support of this view has recently been advanced by Ferrata and Franco,¹⁰ who observed in the peripheral blood and in the spleen of patients suffering from chronic myelogenous leukemia, a type of cell ("hemohistioblast") which had not been recognized as a distinct circulating form in the previous hematological literature. Morphologically, this cell has been identified with the group of tissue cells variously known as "clasmatoocytes" (Ranvier), "resting wandering cells" (Maximow), "adventitial cells" (Marchand), "reticulo-endothelial system" (Aschoff), "hemohistioblasts" (Ferrata), and so forth. Not only

* In the normal adult, the hemogenic activities of the connective tissues are probably confined to the production of some of the monocytes of the blood. The formation of cells other than those normally produced is generally referred to as "metaplasia."

were these cells found in the peripheral circulation, but the presence of typical neutrophilic and eosinophilic granules in their cytoplasm indicated that the connective tissues from which they came were undergoing myeloid transformation. Subsequently, Ferrata^{8, 9} described these cells in greater detail, dividing them into definite groups according to the type of granules and other characteristics which they presented.

Meanwhile Ferrata and Negreiros-Rinaldi¹¹ described the same cells in a case of malaria, noting that they differentiated into monocytes and lymphocytes.

Gasbarrini¹³ found hemohistioblasts in lymphatic leukemia, and Reitano²⁰ in monocytic leukemia, in which cases they differentiated into lymphoid and monocytoïd cells instead of into granular leukocytes.

Hemohistioblasts have been reported by Franco¹² in *Leishmania infantum*, in which they play an important part in the splenic pathology.

Esposito⁶ reported 5 cases of myelogenous and 3 of lymphatic leukemia, in which hemohistioblasts were found. His illustrations picture cells in stages of myeloid and of lymphoid differentiation.

Ferrata also ascribes to the hemohistioblast the potential capacity for differentiation into red blood cells. According to his conception of pernicious anemia, for example, there is in that disease a direct derivation of megaloblasts or primitive erythroblasts from hemohistioblasts.⁷ Direct evidence of this derivation has been reported by Vasiliu,²³ who found hemohistioblasts in the peripheral blood of an infant with pernicious anemia, and observed stages in their differentiation into megaloblasts. Di Guglielmo,⁵ in a study of the blood of mammalian embryos, concluded that the earliest (prehepatic) circulating blood cells arise in the same manner, and calls attention to the similarity in nuclear structure between the primitive megaloblasts and hemohistioblasts. Vasiliu also noted hemohistioblasts in the normal embryo, reporting their presence in the bone marrow of a human embryo of seven months' gestation.

The importance of the diffuse connective tissue in the pathogenesis of a number of diseases in which skin lesions are associated with changes in the hematopoietic organs, has been emphasized by Bétancès,¹ who believes that in these conditions, which he groups among the "*maladies de l'hématopoïèse*," the hemohistioblasts are capable, when irritated, of directly giving rise to granulocytic and lymphoid cells, without necessarily passing through the hemocyto-blast stage.

In these several articles the hemohistioblasts are represented as "*veri elementi mesenchimatici embriali*," comprising a diffuse hematopoietic tissue, which, in morbid processes, undergoes transformation into specific blood cells.

The author has observed hemohistioblasts in 4 cases of chronic

myelogenous leukemia, and 1 case each of lymphatic leukemia, quartan malaria, infantile anemia of von Jaksch, and *Staphylococcus aureus* septicemia.

Blood smears were stained with Wright's stain or the Jenner-Giemsa combination, and by the peroxidase method. For the latter a solution of benzidine in methyl alcohol to which a drop of hydrogen peroxide had been added, was used as recommended by McJunkin,¹⁷ and the preparation counterstained with Wright's stain. By this method all structures which do not give a positive reaction are stained as they normally are by Wright's stain.

The 4 cases of myelogenous leukemia were typical—clinically and hematologically. The total white counts on admission were between 90,000 and 600,000, of which hemohistioblasts constituted a small and variable percentage—not over 5 per cent. Transitional stages were observed between undifferentiated forms and those with typical neutrophilic or eosinophilic granules. In 1 of these cases, which has been followed over a period of about eight months, hemohistioblasts have been constantly present in the blood, although the total leukocyte count has at times been brought within normal limits by roentgen-ray treatment.

The case of lymphatic leukemia was atypical, corresponding to the "leukosareomatosis" of Sternberg. The patient, a boy, aged thirteen years, was acutely ill with fever, cough, left hemothorax, lymphatic and splenic enlargement, and had on admission a sublymphemic blood picture—from 16,000 to 22,000 white cells, with 65 per cent lymphocytes of normal morphology. This blood picture persisted for several weeks. About two weeks before death the white cells rose to 100,000, of which over 90 per cent were atypical lymphoid cells, frequently of the Rieder type. At this time hemohistioblasts were found, though rarely, in the circulation. They contained typical eosinophilic granules—an interesting feature, as the hemohistioblasts previously reported in lymphatic leukemia were of the lymphoid variety. Necropsy disclosed a mediastinal mass in the region of the thymus, involving the left pleura and pericardium, with generalized lymphatic enlargement. Microscopically, the tissues showed the diffuse lymphoid lesions usually found in lymphatic leukemia.

The patient with quartan malaria was acutely ill, and died less than two weeks after the onset of the first symptoms. Jaundice was marked, and there was increasing lethargy, pulmonary congestion and leukocytosis (22,800), with numerous abnormal monocytes, plasma cells and other pathological lymphoid forms. Quartan parasites were numerous. The hemohistioblasts in this case were of the monocytoïd and lymphoid forms, and were frequently phagocytic.

In the case of *Staphylococcus aureus* septicemia the hemohistioblasts were also monocytoïd and lymphoid, and were phagocytic for bacteria. As a terminal event, cells containing as many as

twenty cocci in various stages of intracellular digestion appeared in the circulation. The diagnosis in this case was confirmed by repeatedly positive blood cultures.

In von Jaksch's anemia the hemohistioblasts contained typical myeloid granules.

Morphology of the Hemohistioblasts. The colored illustrations of Ferrata and his collaborators excellently depict the characteristics of the hemohistioblasts. In general the cells are of very large size, irregular shape, possess a single round or oval nucleus with a characteristic reticulated internal structure, likened by Ferrata to a sponge. They have distinct nucleoli, and basophilic cytoplasm in varying amount, with or without granules. Attenuated cytoplasmic prolongations of considerable lengths may extend between other cells of the smear and give rise to bizarre forms. In some instances mitotic figures have been observed. These general characters are modified in the course of subsequent differentiation.

The hemohistioblasts may be conveniently divided into four main groups:

I. UNDIFFERENTIATED HEMOHISTIOBLASTS. These represent the undifferentiated histogenous cells. Their nuclei are distinctly different from those of any normal cell of the blood or the immature parenchyme cells (hemocytoblasts) of the blood-forming organs. The cytoplasm may be non-granular (Figs. 1 and 4), or may contain azurophilic granules and filaments (Figs. 2 and 3). The filaments are fine attenuated azurophilic structures of varying lengths, which Ferrata identifies with mitochondria. Transitional stages may be observed from undifferentiated forms to hemocytoblasts, or directly to granular leukocytes, lymphocytes and monocytes.

II. LYMPHOID HEMOHISTIOBLASTS. This group includes cells with basophilic cytoplasm devoid of granules, and with nuclei which approach those of normal lymphocytes. They represent stages in the transformation of the undifferentiated forms to lymphocytes.

III. MONOCYTOID HEMOHISTIOBLASTS. All stages of differentiation from hemohistioblasts to monocytes are found. The cytoplasm is basophilic, and may contain azurophilic granules of the type found in monocytes. These cells are frequently phagocytic, as observed in cases of malaria and in septicemia. It is possible that the "macrophages" reported by various authors and experimentally produced by Simpson²² belong in this group, and indicate a mobilization of connective-tissue elements.

IV. MYELOID HEMOHISTIOBLASTS. The greatest variety is found in this group. In cases of chronic myelogenous leukemia the following subvarieties may be distinguished:

1. Undifferentiated forms, as in Group I.
2. Cells similar to the above, but containing premature granules of either neutrophilic or eosinophilic type, with or without the presence of typical mature granules as well (Fig. 5). These imma-

even when the amount of cytoplasm is greatly reduced and the cell approaches them in size (Figs. 6 and 7).

In each of these groups are found cells in which the nuclear and cytoplasmic characters vary in degree, indicating successive stages in differentiation.

Fragments of the cytoplasm of hemohistioblasts are frequently found in myelogenous leukemia. They vary in size from that of blood platelets to fragments larger than ordinary leukocytes. They may resemble platelets or polychromatophilic red cells, with which they should not be confused (Castronuovo³). In some instances they contain neutrophilic or eosinophilic granules, or azurophilic filaments, in which cases they may be easily distinguished.

The Oxydase Reaction. The results obtained with the benzidin oxydase stain correspond in every detail with the author's observations with this method on other types of blood cells: in every positively reacting cell the oxydase is apparently confined to the cytoplasmic granules; in every cell devoid of granules the reaction is negative.*

Not all granules; however, give a positive reaction. Those which react positively are the neutrophils, eosinophils and the azurophilic granules of monocytes, myeloblasts† and hemohistioblasts. The granules which react negatively are the basophils,‡ the immature basophilic granules of eosinophils,¹⁴ the metachromatic granules of blood platelets and megakaryocytes and the azure§ granules of lymphocytes.

These results suggest that the oxydase reaction depends upon the type of cell, rather than upon its origin in any particular organ or tissue.

The hemohistioblasts represent a definite type, not to be confused with any other cell of the peripheral blood. Their morphology, especially the characteristics of nuclear structure, is that of connective tissue (mesenchymatous and endothelioid) cells generally. That they are not degenerative forms is evident from their perfectly preserved structure, and their differentiation through progressive, not regressive stages. Their specific characters are gradually acquired, not gradually lost. This is particularly well

* Naegeli¹⁵ and others report positive oxydase reactions in non-granular "myeloblasts." The author's observations corroborate the previous work of Rosenthal²¹ and of Jolly,¹⁶ who states, "Les oxydases paraissent appartenir seulement aux leucocytes granuleux. Les lymphocytes, leucoblastes et myéloblastes ne donnent pas ces réactions."

† Myeloblasts of Ferrata; unripe myelocytes (promyelocytes) of Naegeli.

‡ Some observers report a positive reaction in basophils.

§ Naegeli distinguishes between the "azure" granules of lymphocytes and the "azurophilic" granules of other cells. Jolly and others do not make this distinction. The results of the oxydase reaction show that all granules stainable with azure-eosin mixtures are not identical. In normal blood, for example, the granules of monocytes, when present, react (weakly) positively, while those of lymphocytes react negatively and stain as they normally do with Wright's stain.

illustrated in the myeloid types, in which the few granules which first appear are immature,* as evidenced by their staining reactions.

Discussion. The term "hemohistioblast," as used by Ferrata, refers to the indifferent polyvalent cells diffusely situated in the connective tissues, commonly known as "clasmatoocytes," "resting wandering cells," etc.

The presence of hemohistioblasts in the peripheral blood in the cases herein discussed, and their differentiation into leukocytes and lymphocytes indicate that these blood cells were being formed directly from connective tissue, without the usual intermediate hemocytoblast stage. There was, in other words, a connective-tissue "metaplasia."

True metaplasias of all kinds are due to changes in the environment in which the cells live.² The importance of environmental factors in the initial (heteroplasmic) stages of hematogenesis has received special attention by Danchakoff,⁴ who states: "On the basis of descriptive histogenetic studies it seemed plausible to admit that environment can modify isolated cells; that the metabolic processes of the cells are the resultant of their physicochemical constitution plus physicochemical conditions of the environment (of course hormones, enzymes and so forth are included in the environment), and do not depend exclusively upon their physicochemical constitution; that different substances arise in the cell body (hemoglobin, various specific granules) in polyvalent cells as result of changes, determined by differences in the environment. The existence of cells endowed with various potencies has in consequence been largely admitted. The specificity of the various mature blood cells would thus be brought about by factors extrinsic to the stem cells."

Observations on the organs in leukemic and other conditions have led several authors to the conclusion that the metaplasias occurring therein arise by the local proliferation of histogenous cells, under the influence of extrinsic factors. A detailed discussion of this subject will not be undertaken here. It should be emphasized, however, that the identification of the hemohistioblast as a histogenous cell, and the development within its cytoplasm of specific leukocyte granules, admit of only one interpretation—the connective tissues undergo "metaplasia" by direct differentiation of their cells.

Environmental factors are thus of the same importance and significance in postnatal metaplasias as in embryonic differentiation. Inasmuch as hemohistioblasts acquire the characters of

* Graham¹⁴ considers that the basophilic leukocyte of the blood is a degenerating eosinophile, and these basophilic granules which eosinophiles sometimes contain, are a sign of degeneration rather than immaturity. In the present investigation, however, the presence of other signs of immaturity (basophilic cytoplasm, fewer granules, less differentiated nuclear structure, presence of nucleoli and sometimes of mitochondria), indicates that the cells in question are less mature than those containing only eosinophile granules.

specific blood cells, we must assume that they were potentially capable of this differentiation, although this potency had been latent; and as the type of differentiation is not the same in all cases, the cells must be capable of differentiation in more than one direction, that is, they are "multipotent." Furthermore, when identical cells develop in diverse directions the cause of their differentiation cannot be intrinsic, but must be sought in differences in their environment.

Conclusions. 1. The hemohistioblasts of Ferrata (clasmatoeytes, adventitial cells, resting wandering cells, reticulo-endothelial cells, etc.) play important hemoeytogenic role in myeloid and lymphoid "metaplasia" in various conditions.

2. In pathological processes these cells and their derivatives may appear in the peripheral blood stream.

3. Hemohistioblasts are potentially capable of differentiation into granular leukocytes, lymphocytes and monocytes.

4. The type of differentiation which they undergo is not dependent upon intrinsic cell differences, but is determined by the character of the environmental conditions imposed.

5. A positive oxydase reaction is given by hemohistioblasts only if they contain neutrophilie, eosinophilie or azurophilie granules.

NOTE.—The cases presented in this paper were observed in the medical wards of Bellevue Hospital. Grateful acknowledgment is made of courtesies extended by Drs. Van Horne Norrie, Charles E. Nammaek, Theodore J. Abbott, Eugene F. Du Bois and Herbert B. Wileox, in permitting the author to study and report observations of cases on their respective services.

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LUNG ABSCESS.

REPORT OF THIRTY-THREE CASES.

BY ALVIS E. GREER, M.D., F.A.C.P.,

HOUSTON, TEXAS.

THE incidence of lung abscess has apparently been on the increase during the past decade. From what causative factors this is due we can only conjecture. There seems to be a rather general impression that the greater frequency of nose and throat operations under general anesthesia has had something to do with this increase. The last great pandemic of influenza has had perhaps some influence.

In the present study there are 33 cases of lung abscess. Fourteen cases were selected from our personal records and 19 from the records of the Baptist Hospital and the St. Joseph Infirmary. All of the cases have occurred during the last five years.

Etiology. The *Staphylococcus aureus* was the predominating organism in the sputum. Anerobic bacilli, especially the gas bacillus, have been reported. Twelve cases (36 per cent) followed operative procedures under general anesthesia. Of these, 4 were from operations other than on the throat, 1 from a ruptured duodenal ulcer, 1 from mastoid disease, 1 from carcinoma of the bladder, and the other followed tooth extraction. Seven cases followed tonsil operations, all under general anesthesia. It is significant that 75 per cent of the postoperative cases followed operations on the throat and mouth. In 33 per cent influenza was responsible, in 15 per cent pneumonia, in 2 per cent an infection of the hand, in 2 per cent an injury to the chest wall, and in 12 per cent the etiology was unknown. Therefore, in 64 per cent of the lung abscesses in this series the etiology was from non-operative causes.

TABLE I.

POSTOPERATIVE.		NON-OPERATIVE.	
	Cases.		Cases.
Tonsil	7	Influenza	10
Mastoid operation	1	Pneumonia	5
Fractured jaw	1	Unknown	4
Ruptured duodenal ulcer	1	Injury to chest	1
Carcinoma of bladder	1	Infection of the hand	1
Tooth extraction	1		
Total	12	Total	21

Sex. Males seem to be more often affected than females. In our series there were 17 males and 16 females.

Age. The ages varied from four to fifty-five years. All of the postoperative cases were adults. The greater number of cases occurred in patients of the second or third decade of life.

Location. There was a predilection for location of the abscess in the lower lobes and especially the right lower lobe. This was particularly evident in the postoperative group, of which 75 per cent were in the lower lobes and 50 per cent were confined to the right lower lobe. In the non-operative cases 71 per cent were found in the lower lobes, 38 per cent being in the right lower lobe and 33 per cent in the left lower lobe. The location of the abscess was in the lower lobes in all cases and 75 per cent were in the right lower lobe following tonsil and mouth operations. Because the throat operations were done under general anesthesia, the aspiration hypothesis must be strongly considered. In Jackson's series 62 to 75 per cent of foreign bodies were found to have entered the right primary bronchus. He gave as reasons for this localization the following:

1. The greater diameter of the right primary bronchus; (2) the smaller angle of deviation of the right primary bronchus from the trachea; (3) the situation of the carina to the left of the axis of the trachea; (4) the action of the trachealis muscle; (5) the greater volume of air going into the right primary bronchus.

TABLE II.

POSTOPERATIVE.		NON-OPERATIVE.	
	Cases.		Cases.
Right lung:		Right lung:	
Upper lobe	1	Upper lobe	1
Middle lobe	1	Middle lobe	2
Lower lobe	6	Lower lobe	8
Left lung:		Left lung:	
Upper lobe	1	Upper lobe	3
Lower lobe	3	Lower lobe	7
Total	12	Total	21

TABLE III.

ALL CAUSES.		Cases.
Right lung involved		20
Left lung involved		14
Lower lobes involved		23
Upper and middle lobes involved		11
Right lower lobe involved		13
Left lower lobe involved		10
Total		91
AS TO CAUSE.		
POSTOPERATIVE.	NON-OPERATIVE.	
Right lung involved 7	Right lung involved	13
Left lung involved 4	Left lung involved	9
Lower lobes involved 9	Lower lobes involved	13
Upper and middle lobes involved 2	Upper and middle lobes involved	9
Right lower lobe involved 6	Right lower lobe involved	7
Left lower lobe involved 3	Left lower lobe involved	6
Total 32	Total	57

Moore has reported 202 cases of lung abscess from information derived from questionnaires sent to other throat specialists. Of these no localization was stated in 91 cases. Of the remaining 101 cases, the middle and upper lobes were involved in 32 per cent, the lower lobes in 60 per cent, the right side in 63 per cent, the left side in 27 per cent. This showed a predilection for the localization of the abscess in the right lower lobe. Reports from the current literature are not uniform as to the right lower lobe being the most frequent location for pulmonary abscesses following throat operations. Lemon, Whitmore and Wessler have reported a series of cases in which there were more abscesses in the upper lobes than in the lower lobes following throat operations. In fact, Wessler found the upper lobes twice as often involved. However, the consensus of opinion is that the lower lobes, and principally the right lower lobe, are the favorite locations for pulmonary abscess. In our series of cases there was a decided tendency for the basal lobe, especially the right, to be the place where the abscess most frequently occurred, and this was more apparent in the postoperative than in the non-operative group.

Certain anatomical facts suggest the reasons why the right lower lobe is involved more often in postoperative lung abscess than are other lobes. Heretofore, we have given Jackson's reasons, and they are probably sufficient. However, for further emphasis we shall call attention again to additional outstanding factors. The right primary bronchus rises nearer to the trachea than does the left primary bronchus; it is shorter, wider, and runs downward in a more vertical course; it lies more in line with the trachea, the angle with the median line being 24.8° , whereas, there is an angle of 45.6° between the trachea and the left primary bronchus. The first

branch to the right upper lobe leaves the main stem 1 inch from the trachea, and the first branch to the left upper lobe leaves its main stem 2 inches from the trachea.

Proponents of the aspiration hypothesis are not without opposing arguments favoring embolism as the route for the development of pulmonary abscess. A study of the pulmonary arteries shows that practically the same facts are found to be present as those described regarding the location of the bronchi, because the distribution of the pulmonary arteries is practically the same as the distribution of the bronchi. The pulmonary artery rises from the anterior left angle of the base of the right ventricle at the termination of the conus arteriosus. It is 2 inches long and divides into a right and a left branch. The right branch is lower and larger and descends with the main bronchus to the lower part of the right lung and sends a large branch to the right upper lobe. The left branch is shorter, smaller and occupies a higher position than the right branch.

The lymph glands of the thorax form five named groups with subdivisions: The sternal, the intercostal, the anterior and the posterior mediastinal and the bronchial groups. It is unlikely that infection could travel from the tonsils to the superior deep cervical glands, whose efferents normally pass to the inferior deep cervical glands, and thence to the jugular lymph trunk, and be carried into the lung tissue. In fact, such a course seems to be an impossibility. Van Zwalenburg and Grabfield have shown an association of the pleural cap with early pulmonary tuberculosis and tonsillar tuberculosis. If their ideas are correct, we have an explanation for the extension of bacteria from diseased tonsillar tissue to the upper lobes of the lungs and thence to the lung hiluses.

It is interesting to note that R. H. Babcock found in 1500 cases of lobar pneumonia that the right lung was involved in 52 per cent, the left lung in 35 per cent, and the right lower lobe in 33 per cent, or twice as often as any other single lobe. Haberfeld in 68 autopsies on cancer of the lung found that the right lung was involved in 65 per cent, the left lung in 35 per cent, and that, especially the right lower lobe was the more frequent location for the disease. Rupp, in a series of cases of pulmonary embolism, found that the right lung was affected in 61 per cent in comparison to 39 per cent in the left lung. From these considerations it would seem that other diseases, namely, pneumonia, cancer and embolism attack more frequently the right lower lobe than they do any other part of the lungs. The anatomical position of the right pulmonary artery and the right primary bronchus, and the greater volume of air in the right lung, which is 10 per cent larger than the left lung, causes a greater wear and tear on the right lung than on the left lung. In our opinion these anatomical facts do not disprove the aspiration hypothesis for postoperative lung abscess; they merely point out other avenues for consideration, although much of the accumulated data up to this date points favorably to the idea that aspiration is the

most frequent cause for lung abscess following throat operations under general anesthesia.

Clinical Features. The onset of lung abscess varies from a few days to three or four weeks, and may be abrupt with a hard chill or may follow a period of less pronounced symptoms, such as, malaise, slight fever, pleuritic pain, and dry cough. The acute stage may be fulminating. The patient at first is oftentimes quite septic with high fever, which is subject to decided diurnal fluctuations, the typical step-like fever of sepsis. Chilly sensations and sweating are noticeable, and at times distinct rigors. The cough at first is dry and harassing but, later, is followed by the paroxysmal expectoration of very foul, purulent, occasionally blood-tinged sputum. Sometimes severe pulmonary hemorrhages occur. One of our patients had a copious hemorrhage. The patient may go for hours with little or no expectoration and, then, expectorate from 3 to 8 ounces of very foul sputum. The odor, although not as bad as in cases of pulmonary gangrene, may seem to pervade the whole room. As a rule the patients lie more comfortably on their backs, slightly propped up, and are unable to lie on either the one side or the other. The sputum is purulent and does not separate into three layers on standing as it does in bronchiectasis. Elastic fibers are often found, but their absence means nothing contrary to the diagnosis of lung abscess. There may be some complaint of pleuritic pain. During this acute stage the patient looks sick and prostrated. The pulse and respiration are increased, although the latter is not increased in the same proportion as the pulse is and it is not nearly so rapid as the respiration in a lobar pneumonic patient. If the patient does not succumb during the acute stage, which varies from a few weeks to several months, a subacute stage is approached followed by a chronic stage. At this time the outstanding feature of the case is the paroxysmal expectoration of large quantities of foul-smelling sputum. It is remarkable that the patient does not always show extreme physical weakness during the chronic stage of pulmonary abscess. Of course, these patients are decidedly subnormal physically, but they maintain oftentimes usually good physical vigor. The temperature may be subnormal in the morning and rise to 99.6° to 103° F. in the afternoon. Occasionally the reverse type of temperature, with the peak in the morning, may be seen. The respiration is not greatly modified, but the pulse is moderately accelerated. There is a tendency toward frequent exacerbations of temperature, the temperature falling for a few days following the paroxysmal expectoration of large quantities of purulent sputum. Sweating and chilly sensations are usually present. Generally there is a lowering of the resistance of the patient, and he becomes sallow, loses weight and looks markedly subnormal and often quite sick. The appetite is fickle, and gastrointestinal symptoms, especially a tendency toward diarrhea, are frequently seen. A distinct leukocytosis with polymorphonuclear increase is frequently a symptom.

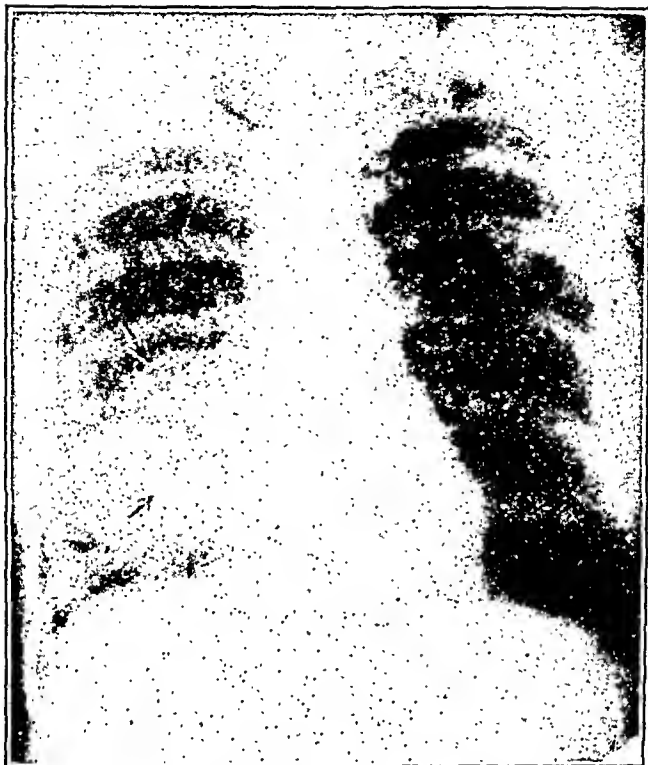


FIG. 1.—Pulmonary abscess involving the right lower lobe.



FIG. 2.—Pulmonary abscess involving the left lower lobe.



FIG. 3.—Pulmonary abscess involving the left upper lobe.



FIG. 4.—Bronchiectatic pulmonary abscess involving the right lung.

Types. Two types of lung abscesses are found: The typical solitary lung abscess and the so-called bronchiectatic lung abscess. The former is a single abscess, while the latter is formed by the fusion of smaller abscesses so that they are connected by small openings, or it may be formed by the irregular extension of a primarily single abscess so that it is then composed of several coalescing compartments. In my opinion it is unfortunate that the term "bronchiectatic lung abscess" has become so generally used because of the evident confusion with bronchiectasis, for there is no etiological similarity between the two conditions. The term "multilocular lung abscess" would more nearly describe the condition. The abscess in the subacute stage is surrounded by a zone of acutely inflammatory lung tissue. In the more chronic stage definite fibrosis takes place. When the abscess in the acute stage is near the pleura a fibrinous, pleural exudate may form, which later organizes into dense fibrous tissue bringing about firm adhesions between the parietal and visceral pleuræ. Ordinarily, however, the abscess ruptures into a bronchus and is discharged therein.

Physical Examination. The physical examination of the chest reveals usually less expansion on the side in which the abscess is located. This may be a general unilateral limitation of movement of the chest wall, or the limitation may be localized to the upper or to the lower chest, depending upon the localization of the abscess. As a rule there is less limitation of movement when the upper lobes are involved. Tactile fremitus is usually diminished over the abscess. When the abscess lies near the chest wall, as is usual when the lower lobes are involved, there may be dullness to ordinary percussion. However, when the abscess is deep-seated, and there is an area of air-containing pulmonary tissue between the visceral pleura and the abscess, light percussion may fail to reveal any dullness, and even heavier percussion may not demonstrate dullness. Generally there is a very definite increase in the pitch of the percussion note. The breath sounds directly over the abscess may be decreased. However, they may be quite harsh at the periphery of the abscess, and large moist rales may be heard in this area. In cases, which are draining through a bronchus, one may hear these large, moist rales extending from the abscess toward the hilus region of the affected side. Whispering pectoriloquy and tubular breathing are usually absent. In the chronic cases all the signs of cavity may be present over the abscess. In our experience this was rarely heard even though we knew from roentgen-ray studies that a large cavity was present.

Diagnosis. Although the history, physical examination, and the clinical course are of great value, the roentgen-ray is indispensable for the correct diagnosis and proper localization of pulmonary abscess. The bronchoscope has some slight usefulness, too.

Acute lung abscess must be differentiated from acute bronchitis,

pneumonia, pulmonary embolism and empyema. Careful consideration of the history, the clinical course, the physical signs, and roentgen-ray should easily rule out these diseases. The differential diagnosis of chronic lung abscess from tuberculosis, chronic bronchitis, bronchiectasis, lung tumors, and syphilis is more difficult than the differential diagnosis of acute lung abscess. In tuberculosis the involvement is more apical, there being frequently marked depreciation of health, a tendency toward progression of the pulmonary signs, which as a rule are absent in abscess, and there is no leukocytosis, and frequent sputum analyses usually reveal tubercle bacilli. In chronic bronchitis the lung findings are more generalized, there being less tendency to paroxysms of purulent sputum, and to exacerbation of increased temperature. Chronic bronchitis is usually secondary to some other disease, and there is no leukocytosis, and the rales are dry. In bronchiectasis clubbed fingers are more frequently observed, the sputum is more abundant and foul, the cough is more affected by posture, the sputum separates into three layers on standing, no elastic fibers are found, and there is no leukocytosis. Lung tumors and pulmonary syphilis may be excluded by the roentgen-ray.

TABLE IV.

INCISION AND DRAINAGE.		ARTIFICIAL PNEUMOTHORAX.		POSTURAL DRAINAGE.	
Cases.		Cases.		Cases.	
Improved . . .	3	Improved . . .	2	Improved . . .	4
Recovered . . .	3	Recovered . . .	4	Recovered . . .	3
Died	2	Died	6	Died	4
Unimproved . . .	0	Unimproved . . .	0	Unimproved . . .	2
Mortality—12 in 33 cases—36.3 per cent:					Per cent.
From incision and drainage					25.0
From artificial pneumothorax					50.0
From postural drainage					30.0
Recovered:					
After incision and drainage					37.5
After artificial pneumothorax					33.3
After postural drainage					23.0

Treatment. In our series incision and drainage gave the best results, showing 37.5 per cent recoveries. Three other cases 37.5 per cent, were greatly improved making 75 per cent of the cases in which incision and drainage were performed that favorable results were obtained. The mortality after incision and drainage was less than after postural drainage alone or after artificial pneumothorax. Artificial pneumothorax was successfully used in 4 cases, 33.3 per cent, and 2 cases 16.6 per cent, were improved, making a favorable outcome in 50 per cent. The mortality, 50 per cent, however, was high. Postural drainage gave the least number, 3, 23 per cent of recoveries. Four cases, 30 per cent were improved, making a total

of 53 per cent of the cases treated by postural drainage favorably affected. The mortality, 30 per cent, was slightly higher than in the cases treated by incision and drainage but considerably less than the cases treated by artificial pneumothorax.

In the early acute cases postural drainage should be instituted, and persisted in, until after the severe symptoms have abated. If the abscess does not rupture through a bronchus, bronchoscopic drainage may be done. This will initiate drainage from the abscess into the bronchus, and will result in a prompt amelioration of the more acute symptoms. In our experience early interference by incision and drainage or artificial pneumothorax is very harmful. After the acute symptoms have passed and the abscess has become more localized a thoracotomy may be performed. Careful study of stereoscopic roentgen-ray plates, combined with physical examination, is necessary. Needling of the abscess is dangerous because of the possibility of infecting the free pleural cavity. By the use of a pneumothorax needle, attached by a tube to a manometer, the presence of pleural adhesions over the abscess may be determined. If adhesions are present, their location may be delineated by inserting the needle in the center of the dull area, and if adhesions are indicated by the absence of free manometric oscillations, the needle should be repeatedly inserted, peripherally, in all directions until free oscillations of the manometer signifies the absence of adhesions. In this way the area of adherent pleura may be very accurately indicated, and the surgeon may without fear of a secondary lung collapse, or of infecting the free pleural cavity, open into the abscess. Artificial pneumothorax should never be performed during the acute stage of the pulmonary abscess, and this is especially true when there are localized adhesions present between the parietal and the visceral pleura. For in such cases excessive coughing may tear the adhesions away from the visceral side causing a serious spontaneous pneumothorax. However, in the chronic, localized pulmonary abscess without pleural adhesions, an artificial pneumothorax may produce good results.

Summary. Lung abscess is more frequent after throat operations than after all other operations. This suggests the correctness of the aspiration hypothesis, there being also definitely known facts to support this view. However, aspiration is not the only way in which pulmonary abscess may develop for influenza, pneumonia and localized infections may be the cause of lung abscess. It may not be amiss to advise strongly against using general anesthesia for nose and throat operations on adults.

RADIUM IN DERMATOLOGY.*

BY A. SCHUYLER CLARK, M.D.,

PROFESSOR OF DERMATOLOGY, NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL; ATTENDING PHYSICIAN, NEW YORK SKIN AND CANCER HOSPITAL; CONSULTING DERMATOLOGIST TO ROOSEVELT HOSPITAL; CONSULTING DERMATOLOGIST TO RUPTURED AND CRIPPLED HOSPITAL, AND CONSULTING DERMATOLOGIST TO BEEKMAN STREET HOSPITAL.

IN 1896 Henri Becquerel¹ discovered radioactive substances through the medium of a burn sustained by carrying some ore in his waistcoat pocket. It was this burn that gave Pierre Curie the idea that radium might prove useful in medical work.

In 1901 Degrais and Danlos had radium put at their disposal for therapeutic purposes but it was not until 1906 that Henri Dominici actually demonstrated that therapy by radium was a reality and that various depths of tissue below the skin could be affected by a process of filtration and that such radium rays had a relatively marked innocuousness for healthy tissues up to a certain point; while, on the other hand, they preserved all their special action on neoplastic tissues.

There are three varieties of rays constantly emitted in the disintegration of radium; that is, alpha and beta electromagnetic rays and non-material electromagnetic pulsations of the other called gamma rays. Alpha rays are of short wave length and are easily filtered out with a thin layer of glass, rubber or almost any other material. Beta and gamma rays are progressively more penetrating and very hard gamma rays can be projected through several inches of human tissues and several centimeters of dense metallic substances.

Beta and gamma rays when they impinge on matter or material produce secondary rays, varying in their intensity with the density of such material, and it is believed that these are the rays responsible for the biological effect of radium on tissues.

In varying doses these rays are thought to either stimulate, inhibit or destroy the reproductive property of cells, especially embryologic cells, reproductive cells, secretory or gland cells and certain inflammatory or neoplastic cells.

In full doses to the skin radium attacks particularly elastic tissue, reproductive cells of the rete, sebaceous and sweat glands, papillæ, and the epithelial lining of the bloodvessels and blood spaces, and if excessive is capable of producing atrophy and telangiectases or even extensive burns comparable to those that can be produced by roentgen-ray.

Any attempt therefore to produce a permanent epilation of the

* Read before the Post-Graduate Hospital clinical meeting, April 11, 1924.

face in hypertrichosis is only to be condemned because of the necessary atrophy that must result to these other tissues in at least some of the cases.

That normal skin tissues subjected to erythema doses of radium do tend to recover more quickly and more perfectly than from a corresponding reaction produced by roentgen-ray, I believe to be true, but this may be explained by the fact that less extensive areas are treated by radium than those for which roentgen-ray radiations are ordinarily used and there is therefore a less extensive area of blood supply cut off.

To state that radium has a selective action on certain pathological tissue is perhaps misleading but Prime² has established that cells devoted to rapid growth and mitosis are decidedly more easily destroyed by radiation than are normal cells which are not mitosing except for purposes of repair, and furthermore, have an adequate equipment of anatomically well formed vessels to supply them.

This explains the excellent cosmetic results that can be obtained in certain types of skin cancer by radium, the cancer cells being destroyed while normal surrounding tissue cells are temporarily inflamed and even stimulated to a process of repair.

The reason why radium is so eminently effective in certain diseases of the skin is due to the fact that we are dealing with surface lesions, most of which can be penetrated by even the hard beta rays, lying as they do within the skin thickness.

Radium plaques, therefore, are eminently suited to most of the lesions and for deeper lesions extending in beneath the skin, plaques combined with the insertion beneath and around the lesions of radium carrying needles, gives a crossfire method with a maximum raying of the lesion itself and a minimum amount to the skin.

Full strength plaques are used from 5 mg. up to 20.52 mg. (a full strength plaque is one in which each square centimeter of plaque surface contains 5 mg. of radium element. A 20 mg. full-strength plaque therefore covers an area of 4 square centimeters).

As the softer beta rays produce so superficial and irritating a reaction in the skin surface, they have been found to be of little use in dermatological lesions and since 1914 my plaques have all had a facing of 0.1 mm. of brass soldered over the face of the plaque in order to cut out these irritating superficial rays.

Practically 90 per cent of all rays emitted are alpha rays, 10 per cent are beta rays and 1 per cent are gamma rays, so that where an absolutely full strength plaque will produce a mild erythema in two to three minutes, a filtration of 0.1 mm. of brass and 1 mm. of rubber will require thirty to thirty-five minutes to produce a similar erythema.

Temporary alopecia is produced by a full strength plaque with a filtration of 0.1 mm. of brass and 0.1 mm. of rubber in fifty-five to sixty minutes, and permanent alopecia results from the application of such a plaque for eighty to ninety minutes.

A faint white level mark will follow an exposure of one hundred and twenty minutes and a quite perceptible but level scar seems to follow such an exposure from one hundred and fifty minutes followed by more or less development of telangiectases with such a filtration.

Foerster³ states that approximately one-half of the beta rays are filtered out by a thickness of 0.05 mm. of platinum, 0.1 mm. of lead, 0.11 mm. of silver, 0.13 mm. of brass and 0.4 mm. of aluminum.

Caldwell and Russ have determined that the intensity of the hard beta rays is reduced to about 6 per cent of their initial value after passing through 1 cm. of epithelial tissue.

One-half of the gamma rays are absorbed by 6.2 cm. of aluminum, 1.4 cm. of lead, and 1.14 cm. of silver.

The intensity of radiation is further reduced by distance, but not exactly I believe in accordance with the inverse square law, that is, doubling the distance reducing the intensity to one-fourth.

The radium needles used are mostly of 5 mg. platino-iridium with wall thicknesses of 0.2 mm. and can be left embedded in soft healthy tissue for two hours with very little reaction and in dense tissue for three or four hours or more.

Where deeper ray effects are required 0.1 mm. of brass and 5 mm. of rubber will produce only a slight skin erythema after two hours of exposure and a similar erythema will result after a six-hour exposure with a filtration of 0.1 mm. of brass, 1 mm. of aluminum and 5 mm. of rubber, with a penetration of a half inch of living tissue.

The substitution of 1 mm. of lead in place of the 1 mm. of aluminum requires an increase of exposure up to eighteen hours for the production of such a faint skin erythema, with of course a penetration of several centimeters beneath the skin.

Radium Therapy in Diseases of the Skin. **Hyperkeratoses.** Clavus and callosities of the feet, two types of lesions that are frequently the cause of pain and discomfort, are so comfortably amenable to treatment by radium that it must be regarded as the method of choice in these lesions.

Soft corns situated as they are, deep in between two toes, show relief from pain in three to five days, and are quite permanently cured in one application with a full strength plaque filtered with 0.1 mm. of brass and 1 mm. of rubber to cut out the secondary rays, and with an exposure of from forty to fifty minutes.

Several callosities of the soles have been painlessly removed without interruption of locomotion after one or two applications of such a plaque for a period of one and a half hours, the lesions having been previously covered for several days with zinc oxide adhesive plaster and soaked and scraped with a dull knife to diminish their thickness and so save time.

A great many verrucous lesions have been cured in one-hour to two-hour exposures without a known failure and in thick warty lesions

extending under the edges and sides of the nails, no other known method seems to me for convenience and results, to compare with radium treatment. No damage is done to the nail bed with consequent distortion and deformity of the nail, and no trace of the lesion is left after healing has been completed.

Verruca plantaris, 7 cases, have responded after plaque applications in a most satisfactory manner with a filtration of 0.1 mm. of brass and 3 mm. of rubber, applied for a duration of two hours. After three or four days the patients are able to walk with much more comfort and the only discomfort from which the patients suffer at all is at or about the twentieth day, at which time the discomfort has never been said to be even as great as it usually was before the application was made.

Leucoplakia of the mouth and leucokeratoses of the lips because of the more or less constant irritation of one kind or another to which they are subjected, are so apt to degenerate into squamous cell lesions that their presence is necessarily a matter of great anxiety to the host as well as to the physician.

Those of a syphilitic nature characterized regularly by atrophy and loss of tissue, are distinctly improved by antisyphilitic measures, and that is of course the first line of attack.

In all types of leucoplakia, smoking should be interdicted, carious and infected teeth should be removed and a most thorough oral hygiene practised. Condiments, very hot or cold and other irritating types of food, should be omitted from the diet, and besides frequent cleansing of the mouth, twice daily the parts may be dried and equal parts of lanolin and rose ointment may be applied and allowed to remain on the lesions as long as possible.

The use of caustics of any kind should be prohibited except of course the possible use of the hot cautery.

Radium, I believe, offers the most convenient and safe method of attack for such lesions that show any sign of thickening, ulceration, or a tendency to degeneration and in the purely smokers type can be usually relied upon to clear up the lesions satisfactorily. All applications should be made with the idea of producing a profound reaction. Glandular enlargements should be carefully searched for, and the patient carefully watched at monthly intervals for a considerable time after the radiation.

In the superficial smokers type, application for sixty minutes with a filtration of 0.1 mm. of brass and 1 mm. of rubber usually result in a smooth shiny eschar, and a complete disappearance of the lesion.

Where there is any tendency to induration or ulceration, at least two-hour application with 0.1 mm. of brass and 3 or 4 mm. of rubber are necessary, and where there is any suspicion of degeneration or much deep induration, in addition to such a plaque 5-mg. platino-iridium radium needles are inserted all around the lesion

about a centimeter apart and diagonally directed beneath the lesion toward a central point, for two and a half to three hours. A cross-fire application is thus obtained which is most effective in clearing up such lesions.

Seborrheic or senile keratoses, occurring as they do mostly on the face and hands of older people, and particularly those who have been exposed to wind, sun and weather, demand a treatment that is effective, and at the same time leaves a good cosmetic result behind.

Radium answers these demands perhaps better than any other known type of treatment except in the very early superficial variety, that can sometimes be cleared up by a resorcin and sulphur ointment.

When the ointment does not promptly clear up these superficial lesions, a fifty- to sixty-minute application of a full strength plaque filtered with 0.1 mm. of brass and 1 mm. of rubber is regularly effective, and that without a mark being left behind to show the site of the original lesion.

1a



1b



FIG. 1a.—Before treatment. Extensive, seborrheic keratoses of the face, with marked degenerations of the nose, eyelid, and outer canthus of eye.

FIG. 1b.—Same, after numerous radium applications.

Deeper seated lesions with more or less chronic inflammatory induration of their bases, or superficial ulcerations, are to be considered more or less seriously, and a ninety- to one-hundred-and-twenty-minute exposure should be made after removing the crusts, resulting in a level white mark left at the site of the lesion, which tends to become more or less nearly the color of the surrounding skin as the months go by.

Very deeply infiltrated lesions or those that have apparently degenerated, should be treated as are frank epitheliomata, and

probably better by a crossfire method with 5 mg. needles inserted from beyond their edges, in beneath the lesions, directed toward a central point, plus a plaque filtered as described above, and both for a duration of from two and a half to three hours.

NEVI OR BIRTHMARKS. Of the nevi the vascular types are much more responsive to radium therapy than are the cellular and pigmented lesions.

Port-wine marks are in the writer's hands more successfully treated by radium than in any other way, but, the end-results are far less proportionately perfect than in the vascular or cavernous types of lesions.

It is more effective in younger individuals, requiring a more careful technic, never to the point of real reaction. It is regularly necessary to stop short of a complete removal of the discoloration, leaving a faint pinkish color, which however is apt to disappear considerably with time.

2a



2b



FIG. 2a.—Before treatment. Port wine nevus on left side of face.

FIG. 2b.—Same, after radium treatment.

Two or, at the most, three applications are required for a given area and a third application occasionally results in the formation of large freckles that persist for many months or even years. At least three months should be allowed to intervene between applications and great care must be taken to exclude all secondary rays. Therefore a filtration of 4 or 5 mm. of rubber is necessary beside the 0.1 mm. of brass.

Fifty to seventy minutes of exposure with a full strength plaque so filtered, depending on the age of the infant is as big an exposure as should be given and in the very dull red deep looking lesions more filtration with a corresponding increase in the dose is indicated. In any case a guarded prognosis should be given even though the results are sometimes really quite satisfactory.

Vascular nevi or strawberry marks, are most successfully treated by plaque applications of eighty to ninety minutes with a filtration of 1 mm. of brass and 4 or 5 mm. of rubber. A faint level whitening of the skin will usually result, especially as more than one application is regularly required. Any considerable erythema is of course to be avoided.

Cavernous angiomata are also successfully treated, especially where a crossfire series of applications can be made from various areas of the circumference, directed toward the center, in order that too many rays may not have to pass through any given area of the skin overlying the lesions.

3a



3b



FIG. 3a.—Before treatment. Cavernous angioma, left side of face; baby, six months old.

FIG. 3b.—Same, after radium treatment. Two years, eleven months old.

At least 0.1 mm. of brass, 1 mm. of aluminum and 4 or 5 mm. of rubber should separate the skin or mucous membrane from the surface of the full strength plaque, in order that long exposures of four to six hours can be made to get a sufficient volume of hard beta and gamma rays projected within the mass to produce an inflammatory reaction of the lining membrane of the deep-lying bloodvessels and spaces.

In lesions of the cheek, crossfire plaque or tube applications from without and within the mouth can be made, remembering that the dose from the mucous membrane side should be about one-quarter less than that through the skin. Three months should be allowed to intervene between treatments. In one case under con-

stant observation a shrinkage seemed to keep up for a period of almost six months after the last radium application had been made.

Big lesions require the additional use of 5 and 10 mg. platino-iridium needles inserted around the lesions at a distance of 1 and 2 cm. from each other, but should not be left *in situ* longer than three to four hours.

Foerster³ speaks enthusiastically of the treatment of strawberry marks and cavernous angiomata, but seems not to have obtained good results in the treatment of Port wine nevi.

Pfahler,⁴ Neweomet,⁵ and Robert Abbe⁶ have also been successful in the treatment of these lesions with radium.

Lymphangiomata, three cases, have been successfully treated by radium plaques with a filtration of 0.1 mm. of brass and 4 mm. of rubber for a duration of one hundred to one hundred and ten minutes. The lesion of the skin recurred at one edge but that responded to a second treatment including a surrounding area of skin 1 cm. beyond the lesion. The two mucous membrane lesions cleared up after two applications each for a period of eighty minutes.

Moles, pigmented nevi and pigmented hairy nevi, because of the involvement of the rete and papillary layers of the skin cannot be removed without some resulting scar. Diathermy, electrolysis, or carbon dioxide snow can accomplish their removal so much more quickly than can radium, which to be effective, would have to be pushed to massive destructive doses, that radium is certainly not the method of choice in these lesions, unless they are showing signs of degeneration.

Three cases of malignant melanomata have been treated by very big massive doses. A lesion of the forearm rapidly growing, the size of a 50-cent piece, has remained well for a period of five years. The resultant scar was excised in order that a careful microscopical search of all the scar tissue might be made, and no sign of any recurring malignancy could be demonstrated after a most careful and painstaking search. Another lesion on the forehead is well after four years, but one lesion on the toe of a woman was followed by metastatic lesions in the inguinal glands after a few months and the patient died. An amputation had been advised before radium was even considered.

Even with this inconsiderable experience with radium in such lesions but a bigger experience after extensive surgical excision, the writer would prefer to take a personal chance with radium than with surgery. Theoretically an extensive endothermy operation with the bipolar method of Wyeth, should be considered as a sane method of attack, but after all much depends on whether or not any metastatic involvement has or has not already begun. When it has, any attempt at removal in any way is of course useless. I am of the opinion that the time to attack these lesions is when they are quiescent and if possible before any metastases have occurred.

HYPERTROPHIES. Keloids and hypertrophied scars are well taken care of by radium in the form of full strength plaques, and this particularly applies to young lesions that have not existed longer than six months. Old, hard fibrous lesions had probably better be excised where suitable tissue is at hand for primary suture without deformity, followed by radium exposures beginning at about the seventh day, to prevent a recurrence after excision. In these old lesions destructive doses of radium must be used if at all and although a soft pliable scar results, it does not seem to be the ideal method.

Four or five millimeters of rubber tissue should be used over 0.1 mm. of brass for a period of about ninety minutes (one-third less for very young children).

One such application frequently suffices to prevent a reformation of the keloid.

Young keloids require 2 and possibly 3 radiations at two-month intervals, with a filtration of 0.1 mm. of brass and 5 mm. of rubber, plus an added 1 mm. of aluminum, for a period of two to six hours, depending on the thickness of the lesion.

In any case, never more than the faintest erythema of the overlying skin should be produced, because of the tendency to a resulting telangiectasis.

A soft pliable, level, white skin or scar remains at the site of the lesion.

The rather severe pain that sometimes accompanies such keloidal formations, is quite regularly relieved by the first application.

Acne keloid has been reported by several authors as successfully treated by radium, but I have had no experience with these lesions except in the use of roentgen-ray.

GRANULOMAS. Granuloma annulare (two cases), cleared up quite promptly after a single radiation of seventy minutes with 0.1 mm. of brass and 2 mm. of rubber.

Pyogenic granuloma (one case) on the upper lip the size of a five cent piece, and $\frac{3}{8}$ of an inch in depth, cleared up after a single dose of three and a half hours with a filtration of 0.1 mm. of brass and 1 mm. of rubber, and with a better cosmetic result than I have ever previously obtained with either cautery or curettage and silver nitrate stick.

Granuloma fungoides, blastomycosis, and sporotrichosis, should of course be as favorably influenced by radium as it is said they are at times by roentgen-ray, but the extent of these lesions has prevented any attempt on the writer's part to employ radium in their treatment.

For lupus vulgaris radium has proven to be, it is believed, one of the best means of attack in this country where we have not the Finsen light at our disposal. Two cases involving the lower half of the nose are well—1 now for eight years, and several cases around

the mouth, 2 with extensions on the mucous membrane, are healed and present only soft pliable scar tissue, with some telangiectases at the site of the skin lesions.

Small doses are entirely inadequate and plaque applications corresponding to what should be 4 erythema doses, if one can speak in such terms, are necessary.

Beta rays are, therefore, the rays of choice and two- to three-hour applications are given with a filtration of 0.1 mm. of brass covered by only a few layers of rubber tissue. Successive applications frequently have to be given, and there is no advantage to be gained by a longer period between applications than six to eight weeks.

4a



4b



FIG. 4a.—Before treatment. Old, persistent lupus vulgaris, right side of face.
FIG. 4b.—Same, seven weeks after treatment with radium.

Lupus vulgaris and tuberculous ulcerations of the mucous membranes can often be healed by such a massive dose of radium, of course, with considerable discomfort to the patient. But comfort and cosmetic results are the least of one's considerations in an effort to heal lupus vulgaris lesions anywhere.

Tuberculosis verrucosa cutis lesions have also been healed in several cases, but here again big skin reactions from massive doses are necessary.

In Lupus erythematosus I cannot agree with the majority of authors that radium is ineffective in the fixed or discoid type of lesion so frequently seen on the faces of our patients. And this after a very considerable personal experience with this disease.

The disseminated type is a different proposition, portending a serious toxemia of some kind somewhere, and in patients who sur-

vive, the lesions can and do spontaneously clear up usually, without any scarring.

In the discoid type any spontaneous healing always results in scarring.

5a

5b



FIG. 5a.—Before treatment. Thick, crusted, discoid lupus erythematosus in large patches scattered over the face.

FIG. 5b.—Same, after two and three radium applications to individual lesions.

6a

6b



FIG. 6a.—Before treatment. Lupus erythematosus, fixed type, with a moderate amount of infiltration.

FIG. 6b.—Same, after treatment. One series of radium exposures.

Foerster³ seems to have possibly explained Highman and Rulison's⁷ hypothesis as to the comparative incompatibility of Lupus

erythematoses and radium therapy in the relation of pathology and effect of treatment, because of the similar end-result in both. He suggested that it may be argued that by the use of radium results are obtained analogous to those that result after the spontaneous healing of lupus, namely, atrophy and telangiectases, and that after roentgen-ray treatment, elastic tissue having been destroyed and vessels dilated, lupus lesions seem to retrogress and heal. This they actually seem to do, for no result can be hoped for short of an atrophy by the radium application.

Applications almost always have to be repeated to produce this atrophy and healing. Such repeated applications of sixty to seventy minutes filtered with 0.1 mm. of brass and a few layers of rubber tissue have healed such extensive lesions as involvement of almost the entire nose, or patches across the bridge of the nose with extensive involvements of both cheeks. Numerous large and small thick infiltrated patches on other parts of the face and head have also healed. True it is that some lesions tend to recur at the edges of the scar, but the inclusion of a considerable area of skin beyond the lesion in the radiated area has apparently resulted in a number of lesions remaining permanently well.

SKIN CANCERS. Krompecker, in 1900, recognized a type of cancer arising from the basal cells of the rete and in 1904 Bloodgood published an important article in which he demonstrated two important types of skin cancer, that is, the basal-cell group of Krompecker and the prickle-cell type, composed of large cells that had retained their prickles, were early destructive and grew rapidly, tended to metastasize and have a general malignancy; in contradistinction to the former group, which grew slowly, did not metastasize and were of a local malignancy only.

Degrais, a dermatologist, in 1901, treated the first case of skin cancer with radium. Since that time thousands of cases of basal-cell epitheliomata have been so successfully treated by this agent that today, I believe, there is no question but that the preponderance of opinion among surgeons who are familiar with its use is in favor of radium as the method of choice in the treatment of such lesions. This would be true for cosmetic reasons alone to say nothing of the convenience to the patient and the end-results.

In the treatment of the prickle-cell variety of lesion there is no such unanimity of opinion owing to the tendency of the draining lymph nodes to be involved, but, occasionally, brilliant results have been obtained by bold radium operators in epithelioma of the lower lip and buccal mucosa, coupled with extirpation, or irradiation of the draining lymph nodes. This has been accompanied by such good cosmetic results that it is conceivable that with an improved technic radium, alone or combined with surgery, may yet become the method of choice in this more serious type of lesion.

Cancers of the skin may be divided more or less according to their degree of susceptibility to radiation, into:

1. Basal-cell epitheliomata.
2. Lymphosarcomata.
3. Sarcomata.
4. Prickle-cell epitheliomata.
5. Nevocarcinomata (malignant mole or melanoma).
6. Epithelial carcinomata originating in sebaceous and sweat glands.

Basal-celled epitheliomata present the following more or less common clinical types as described by Hazen:⁸

- (a) Superficial, psoriasis-like type.
- (b) Superficial, rolled-edge type, with central ulceration or a fungus growth in center.
- (c) Deeper ulcerating type.
- (d) Superficial, nodular type.
- (e) Deep, nodular type, frequently taking form of infiltrated plaques.
- (f) The morphea-like type.
- (g) Cicatricial type, healing in center with nodules or ulcers at edge.

Usually, the location, type, character and growth serve to help us distinguish the basal-cell type but, occasionally, a really comparatively benign-looking lesion may turn out to be of the metastasizing type and one must be constantly on the lookout for a possible, rapidly developing recurrence or a beginning glandular activity. Rarely have reports come in of basal-cell tumors developing typical basal-cell metastases. One of my own cases, at the age of eighty-four years, two and a half years after removal of an apparently classical basal-celled epithelioma of the left ala of her nose developed a metastatic lesion in her left cervical region.

Fortunately, the great majority of epitheliomas of the face where a good cosmetic result is of major importance, are of the rodent ulcer or basal-cell type, with the pronounced exception of cancer of the lower lip, where absolutely the reverse holds true.

Cancers of the upper lip are usually basal-celled as are those of the lobes of the ear. Malignant lesions of the skin of the body and extremities are more frequently of the prickle-cell variety and frequently develop on tuberculous, specific or other chronic ulcers and on seborrheic or senile keratoses, warts, moles, angiomas and nevi that are subject to more or less constant irritation, such as picking and scratching.

Leucoplakia of the buccal mucosa and lips are frequently forerunners of prickle-cell cancer in these regions.

The basal-celled type of lesion is the one that has especially interested the writer as a dermatologist and particularly those of the rodent ulcer type. These are said to occur on the face above an

imaginary line connecting the angles of the mouth with the lobes of the respective ears. Fortunately, the very great majority of skin cancers in this area are of this type, for it is here that a good cosmetic result is a matter of considerable importance, and radium gives this end-result par excellence. Particularly is this true in lesions around the eyes, of the eyelids themselves, the ears and the ala of the nose.

Francis Carter Wood⁹ estimates that the majority of human cancers require 5 erythema doses of radiation to destroy them. But, he adds, it is understood that the basal-cell tumors of the face are excepted, since it has been known for many years that most of them will disappear with 1 or 2 erythema doses, provided they have not invaded cartilage or bone, in which case a much higher dosage is necessary to be effective.

None were controlled by biopsies as lesions were on the face and cosmetic results had to be considered.

Upwards of 200 cases of skin cancer have been treated by the author since 1912. Only 10 bad results are known and, of these, 6 were cases of squamous-cell epithelioma about the face or mouth that were inoperable or had refused operations and a good result could not have been even hoped for. Of the remaining 4, 1 was an involvement of the whole lobe of the ear, 1 involved the periosteum of the right temporal bone, 1 the periosteum of the left malar bone and the fourth was an accidental leaving of a protecting sheet of lead between the eyelids and eyeball for several days with the loss of the eye. The malignant lesion had involved the periosteum as well as the inner canthus of the eye and promptly recurred. The patient lost his life under the anesthetic given for the enucleation of the eye and the removal of the periosteal lesion.

Fifteen lesions of the eyelids have been treated with good success in 14, the one failure being the case just described.

Four cases of extensive involvement of the cartilage of the ear have been treated and three of them are well with excellent cosmetic results.

Of all the cases, 13 are known to have remained well for seven years; 16 for five years and 86 for upward of three years.

Twenty-one cases have required a second application to clear up the lesion or have recurred, but healed promptly under additional applications.

The best results, undoubtedly, have been obtained in the cases treated during the past three years owing to the frequent combining of 5 mg. radium needles, inserted around or beneath the lesions with a suitably filtered plaque applied to the surface. Certainly, the cosmetic results have been better, owing to the fact that this combined method required less exposure through the surface from the plaque.

It may be laid down as a rule, I believe, that lesions that do not

clear up or nearly so under one single, intensive dose and certainly, after a second effort, should be promptly referred to the surgeon for surgical or endothermic removal. Such lesions probably are not of the basal-cell type or have involved the periosteum or are of that unusual basal-cell type, very rare and about which we know very little, which is exceedingly resistant to radiation.

7a



7b



FIG. 7a.—Before treatment, nodular, basal-celled epithelioma.

FIG. 7b.—Same, after radium treatment, showing cosmetic result.

8a



8b



FIG. 8a.—Basal-celled epithelioma, recurring after operation, extending into inner canthus of eye.

FIG. 8b.—Same, after radium treatment, healed four years.

A. The superficial, psoriasis-like type of lesion can be healed without scar by a full-strength plaque exposure, filtered with 0.1 mm. of brass and 1 mm. of rubber for a duration of sixty minutes.

B. The Superficial, rolled-edge type, with a central ulceration or a fungating growth in the center and D, the superficial, nodular type, require a two-hour exposure with 0.1 mm. of brass and 2 mm. of rubber.

C. The deep ulcerating type and E, the deep nodular type demand the insertion of 5 mg. platino-iridium needles, inserted from beyond the circumference beneath the lesions, directed toward a central point at intervals of 0.5 to 1 cm., plus a full-strength plaque filtered with 0.1 mm. of brass and 5 mm. of rubber, both for a duration of three hours or more.

9a



9b



FIG. 9a.—Before treatment. Ulcerating, basal-celled epithelioma of nose.

FIG. 9b.—Same, healed by radium, four years.

10a



10b



FIG. 10a.—Fungating basal celled epithelioma of temple, size of a silver dollar.

FIG. 10b.—Same, healed by radium, three years.

Degenerated, thick, pigmented nevi and melanomata require a similar attack but, with a duration of both for a period of from four to six hours *with* an additional 0.5 mm. of aluminum filter placed on the face of the plaque.

It would seem that lesions involving the periosteum had better be treated surgically or by a combination of surgery and radiation.

Nodular lesions of the eyelids are successfully treated by the

insertion of 5 mg. radium needles placed immediately beneath them at 0.5-cm. intervals for periods of from two to four hours.

It is believed that a fertile field for bold radium operators lies in the treatment of carcinomas of the lower lip and lesions within the mouth. In these cases the coöperation of a surgeon is always essential; any glandular enlargement should demand surgical removal, and that completely, of the submaxillary and even perhaps of the cervical regions.

Two of my cases stand out so well that they will bear reporting. Both had refused operations on the lip and tongue respectively, both accepted surgical removal of glands that felt stony hard in one of their submaxillary regions and, incidentally, a careful search of the removed glandular tissue of both failed to show any malignant involvement. Both had pyorrhea and carious teeth and a dirty mouth condition. Both had been seen by several surgeons and pronounced malignant lesions.

The lip case has remained well for two years after a crossfire from the mucous membrane and skin surfaces and needles imbedded in the substance of the lip.

The tongue case was a very extensive leucoplakia with a carcinomatous degeneration of the right half, near the midline, the size of a hickory nut. This lesion healed promptly with some slight discomfort after combined needle and plaque applications and has remained healed for one year. Two other small, beginning degenerations of his leucoplakia at distances of at least $\frac{1}{2}$ inch from the old lesion, due to irritation from his continued excessive smoking, healed promptly after the use of needles alone.

A therapeutic test treatment of 10 salvarsan injections at three-day intervals (3.4 gm. in all) had, previous to the treatment, failed to make any appreciable effect on the lesion.

Brewer,¹⁰ believes from statistics that he had collected "that the results of surgical treatment of lip cancers are superior to those as yet obtained by radium. On the other hand, in cancers of the cheeks the results obtained by radium are so evidently in advance of those obtained by operation that until it can be demonstrated by a series of well observed three- or five-year cases that operation will give equally good results, all cancers arising in the mucous membrane of the cheek should be treated by radium."

Broders¹¹ gives food for thought in lip cases when, in a resume of 537 lip cancers treated surgically, he reports a mortality of 82.6 per cent in patients with metastases and of 23.73 per cent in those in whom no metastases were demonstrated. He states that no patient with cervical lymph nodes involved or with more than one group of any lymph nodes involved had been reported living.

Lymphosarcomata should respond at least equally well to radium as to the roentgen-ray but, I have had only one experience with the latter.

Xeroderma pigmentosum (one case in a man, aged twenty-three years) has been carried comfortably and well through a period of five years, by the internal administration of arsenic at intervals and the removal of many degenerated lesions on his face, as they appeared, by radium plaque applications with most excellent cosmetic results.

Five cases of roentgen-ray degeneration in old, chronic extensive roentgen-ray burns have been more successfully taken care of by radium applications and the frequent use of equal parts of lanolin and cold cream than by any other of the various methods that have been suggested.

11a



11b



FIG. 11a.—Before treatment. Xeroderma pigmentosum Many degenerated lesions.

FIG. 11b.—Same, after radium treatment.

Only exceedingly small doses of twenty-five minutes with a filtration of 0.1 mm. of brass and 1 mm. of rubber are necessary to clear up early superficial nodular or ulcerating degenerations as they arise. Larger doses are productive of long standing, sluggish ulcers that are exceedingly painful.

Cheilitis exfoliativa of both lips; two extensive cases have been cleared up after repeated, filtered plaque applications.

Sarcoid of the Darrier-Roussy type; 2 cases remain well, 1 after four years and 2 typical cases of Paget's disease of the nipple, declining operation, are well after three years and one year respectively. They are, of course, under a most careful and frequent observation.

Three-hour applications with a filtration of 0.1 mm. of brass and 5 mm. of rubber are necessary in the treatment of the sarcoid lesions as these lesions are quite deeply seated in the skin.

Summary. Radium seems to stand out preëminently as the method of choice in the treatment of basal-celled epitheliomata, vascular nevi, warts of various kinds, leucoplakia of the mucous membranes, keloids and seborrheic keratoses and probably, in lupus erythematosus and lupus vulgaris.

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THE GASTRIC SECRETION: ITS BACTERICIDAL VALUE TO MAN.*

BY HENRY J. BARTLE, M.D.,
PHILADELPHIA.

WITH A REPORT OF BACTERICIDAL EXPERIMENTS.†

BY MALCOLM J. HARKINS, V.M.D.
PHILADELPHIA.

WE have all been impressed; it is quite likely, by the oft repeated statement, (made in lectures, in text-books, and in writings of men interested in gastroenterology), of the so-called protective power or bactericidal power of the gastric juice. The acid secretion of the stomach, with its pepsin enzyme, is given credit for an ability to destroy swallowed living bacteria almost universally and unequivocally; and yet, if this be so, whence comes the prolific and varied bacterial flora of the gut tract? Surely not entirely by infection introduced through the anus; and more surely not even in small part can infection by way of the blood and lymph streams be given credit for the luxuriant growth of colonic bacteria. It must come by way of the stomach, from the mouth.

It has been said by Breslau in 1866, and again by Bass¹ in 1922 that within three to six hours after birth, the meconium (which

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Billroth in 1874 showed to be sterile) becomes infected, and thence onward the infant's previously sterile gastrointestinal content harbors bacteria. Whether it be for ninety hours, or ninety years, until that complex biochemical structure, his body, resolves itself into the elementary constituents of which it is composed, his gut tract remains infected constantly.

We do not know what the degree of gastric acidity is of the newborn babe. We have read, but we cannot quote the authority, however, that babies run a high gastric acidity. From personal experience in testing, fasting and digesting extractions in children from three to six months of age, of the true or pseudo-congenital hypertrophic pyloric stenotic group, we know that the free hydrochloric acid runs about as in the adult, from 10 to 40, rarely more; and that the total acid values range from 25 to 75, rarely higher, except where there is a decided stasis with the formation of excessive amounts of butyric acid. So that we think it is quite safe to assume that the function of the stomach in elaborating free hydrochloric acid and pepsin is taken up quite early in extra-uterine life.

It is probable that the infant's stomach takes on the function of elaborating gastric secretion before the first mouthful of colostrum is swallowed; and that the changing of the blood stream from the ductus venosus to and through the portal veins may have a great deal to do with the automatic starting of this secretory act. We shall welcome suggestions relative to this point. However, it may be that this function of acid and enzyme secretion is somewhat long delayed and that those organisms constituting the so-called normal flora of the bowel, entering early, begin their residence and that thenceforth, following the axiom promulgated by Noeggerath the host being "once infected remains always infected."

The history of the search for the truth as to the power of the gastric secretion to destroy living bacteria begins with, and is intimately associated with, the history of the study of the bacteriology of the feces, dating back beyond 1846.² Uffelmann in 1881 found in the stools of infants very thin mobile rods, cocci and strepto-bacilli. Later Escherich (1886) using agar gelatin, cultured bacteria, and tried to differentiate normal saprophytic bacteria from pathogenic bacteria in the stools, and described the *Bacterium coli* and *Bacterium lactis aërogenes*. In 1899 the *Bacillus bifidus communis* was first described by Tissier³ and was seen to be the commonly infecting organism in breast-fed babies. Later (1900) Moro described the acidophilus bacillus as the commonly infecting organism in the bottle-fed babies.

This, then, seems to be the first observation that the type of food could influence the intestinal flora. Evidently bacteria of certain types could survive passage through the gastric secretion of these infants. Feeding sterile food was tried by Sucksdorff (1886); by

Britzu (1895); Gilbert and Dominici (1894). These investigators found that the number of bacteria was reduced by such food. But Stern (1892), Adrian (1895), Eberle (1896), and Ballner (1904) did not find that sterile food reduced the number of bacteria.⁴

There follows a long list of investigations, from the early work of De Jager (1897), to the most recent work of Rettger and Cheplin,⁵ with the one aim in view and that to change the type of the intestinal flora by feeding certain groups of bacteria—those found in buttermilk, sour milk, kefir, koumiss, matzoon and by the administration of *Bacillus bulgaricus* and *Bacillus acidophilus*. To do this it was necessary to implant these organisms in the gastric secretion. How well this has been accomplished you all know. The work of Norman⁶ (1922) is along somewhat different lines, for he introduces *Bacillus acidophilus* from below, and combines the administration of lactose both by mouth and by rectum. A few years ago Lyon and Bartle went a step further by introducing *Bacillus acidophilus* directly into the duodenum by way of the duodenal tube, because they feared that many of the bacteria were being killed in their passage through the stomach.

In 1894 Cassaet⁷ made some experiments with gastric juice taken from a patient having a permanent hyperchlorhydria. He allowed the secretion to remain in open test-tubes for a period of ten days, and found it still sterile at the end of that period. He then inoculated the tubes with *Bacillus lactis aërogenes* and *Bacillus coli*, but still they remained sterile. Upon neutralizing the hydrochloric acid and again implanting *Bacillus coli*, the tubes became cloudy within twenty-four hours and cultures yielded growths of *Bacillus coli*. His conclusions were as follows: (1) That the gastric juice when sufficiently acid, that is to say, corresponding to an artificial acidity of 2 per cent, is an antiseptic medium for certain species of bacteria such as *Bacillus lactis aërogenes* and *Bacillus coli*; (2) that *Bacillus coli* is more resistant than *Bacillus lactis aërogenes*; (3) that at 1 per cent, hydrochloric acid slightly retards the evolution of *Bacillus coli*, but that this latter brought back later into a suitable medium, rapidly recovers all its properties; (4) that it is useful to employ a 2 to 4 per cent hydrochloric acid lemonade in cases of *Bacillus coli* infections, as well as typhoid infections.

NOTE.—These high percentages are never attained in the human stomach, for even 100° of free acidity is only equal to 0.365 per cent HCl.

Mutch,⁸ in an article published in 1914, says: "Unless the acidity is extremely diminished, only a few of the organisms can flourish. Even with marked hypo-acidity, gastric stasis is necessary for free bacterial action. The organisms which grow best in moderately acid media are *Bacillus acidophilus* of Moro and yeast. They can live on a medium which is acid to Congo red. Both ferment carbohydrates, the former producing lactic acid, the latter gas.

Gastric fermentation is marked when motor disability and hypo-acidity occur together."

Inkster and Gloyne⁹ in 1921, reported their results of experiments conducted with gastric juice from normal individuals, to test its bactericidal action on tubercle bacilli. They found that after ninety minutes exposure in a test-tube the bacteria in sputum were still viable, and that those obtained from mouth washings retained their viability after one hundred and eighty minutes exposure. From this they conclude that "the protection against the tubercle bacillus afforded by the gastric secretion is apparently by no means perfect. But it must be remembered that the dilution of the contents and the motor activity of the stomach probably play a large part in the mechanism of protection, and these latter factors cannot be satisfactorily experimented upon *in vitro*." These results are in agreement with the conclusions arrived at by Allen MacFayden¹⁰ under different conditions and with bacteria other than *Bacillus tuberculosis* as long ago as 1887.

Schonbauer in 1922,¹¹ worked with streptococci, hydrochloric acid and pepsin. He used a 3 per cent HCl bouillon and recovered living streptococci twenty-four hours after inoculation. But 3 per cent HCl bouillon to which 2, 3, 4, or 5 per cent pepsin had been added, failed to give a viable organism after an exposure of twenty-four hours. From this experiment it seems that the bactericidal action of the gastric juice is largely dependent upon its pepsin content.

Koploff,¹² in 1923 concluded that there is no correlation between high acidity in the stomach and low bacterial numbers, or *vice versa*. Streptococci were found associated with high as often as with low gastric acidity. The fact that the bacterial count on the fasting contents is usually considerably lower than during the process of digestion, indicates that little or no multiplication of bacteria takes place when the stomach is relatively at rest; and that the greater numbers found during digestion are introduced with the food and saliva.

In this he is in disagreement with Cotton,¹³ who claims that the stomach acts as a focus of infection, and through invasion of its wall by the bacteria, has its secretory function lessened or lost, thus allowing its flora to flourish unhindered. With the use of vaccines he claims to re-establish the secretion of hydrochloric acid and the elimination of the infecting organisms.

Even this short and incomplete historical resume of the literature on this subject would be incomplete without reference to the splendid paper by Knott,¹⁴ which appeared before our work was begun, but was not reviewed until after our experiments were completed. A perusal of that paper will show how closely our results parallel those of Knott, except that he found that *Bacillus coli* are more resistant than the staphylococcus to the action of the gastric juice. Always, however, the question of the resistance of the particular

strain with which the investigator is working must be considered, and due allowance must be made for seemingly apparent contradictory findings. He refers to the work of Bunge¹⁵ in 1890, who was the first to express the opinion that hydrochloric acid has an antiseptic as well as a digestant function. He also quotes Hurst¹⁶ who studied various clinical conditions in relation to the absence of hydrochloric acid in the gastric secretion. He concludes that a constantly high level of free acidity tends to protect the individual against infection; that pepsin, combined hydrochloric acid and the organic acids play no part in affording protection.

A Review of Bacteriological Findings. There have been thousands of cultures taken of the bile of many hundreds of cases, and it was hoped at first that the result of the bacterial studies of these specimens could be analyzed, and that a complete statistical report could be prepared. But the volume of work was too great for the amount of time that could be spared at present, and we think that the same purpose will be served by taking 200 consecutive cases and giving the cultural statistics as we found them in this group. On the 200 cases there were 299 cultures made—many of these were repeated for the reason that (a) either the first culture was sterile, contaminated, or unsatisfactory because *Bacillus coli* grew so luxuriantly that it was feared that some less rapidly growing organism might have been missed; or (b) to check up after a period of weeks had elapsed to ascertain if a subsequent culture would give the same results as the first one.

Table I shows the result of this investigation.

TABLE I.—BACTERIOLOGICAL STATISTICS OF 299 DUODENAL CULTURES MADE ON 200 PATIENTS.

		Times.	Percent- age.	Total times.
Sterile		30	= 10	
Streptococci with staphylococci		35	= 12—	
Streptococci with <i>B. coli</i>		27	= 9	
Streptococci with staphylococci and <i>B. coli</i>		12	= 4	
Staphylococci with <i>B. coli</i>		15	= 5	
Streptococci	{ Hemolytic, 30 = 10% Non-hemolytic, 24 = 8%	54	= 18	128 (Streptococci)
Staphylococci	{ Aureus, 40 = 13% Albus, 12 = 4%	52	= 17+	114 (Staphylococci)
<i>B. coli</i>		52	= 17+	106 (<i>B. coli</i>)
Pneumococci		2	= 1—	
Yeast		3	= 1	
Contamination		17	= 6+	
		299	= 100	

Giardia were found three times in 200 patients (1.5 per cent incidence).

Organisms found in bile as well as in—	Tooth socket.	Tonsil.	Tooth and tonsil.
Streptococci { Hemolytic	10	3	3
	1	0	0
Staphylococci { Aureus	1	1	1
	1	0	0

Inasmuch as this study endeavors to answer the important question: What protection does the gastric secretion give to man against invasion of his gut tract and biliary passages by infecting organisms?—it was thought wise to study the cultural returns obtained in practising non-surgical biliary drainage as advanced by Lyon¹⁷ in an endeavor to ascertain what effects the various motor and secretory types of stomachs would show on these cultures. At the same time an endeavor was made to reach some conclusion as to the source of the organisms found—whether it be the bile, the duodenum, the stomach secretion washing out while the drainage was in progress, the bowel below by reflux of its contents, or the tube. With these points in mind we turned to the records of 200 cases, and believed that this number should suffice if an answer were forthcoming.

The question of biliary regurgitation was investigated, hoping that some light would be cast upon the question of the normal or abnormal physiology of this act from the bacteriological aspect. It was assumed that if bile were abnormally regurgitated from the duodenum to the stomach a like process could be occurring beyond the duodenum—in the jejunum and ileum—and that perhaps *Bacillus coli* was being brought up from remote portions of the gut tract to be recovered in the duodenal culture. All cases, therefore, in which biliary regurgitation was noted as present or absent, either fasting or digesting in the fractional examination, or in which *Bacilli coli* were recovered, were gone over with this in mind. Our records were incomplete in 50, so that the analysis was based on 150 cases. Seventy-two of the 150 cases (48 per cent) showed regurgitation; and in only 28 of these 72 cases (39 per cent) was the *Bacillus coli* recorded as found in the duodenal culture, either alone or in company with some other organism. The other 44 cases (61 per cent) having regurgitation of bile, gave no *Bacillus coli* on culture.

There were, in all, 57 cases (38 per cent of the 150 cases) which gave a positive return of *Bacillus coli* on one or more cultures. Twenty-eight of these 57 cases showed biliary regurgitation, whereas 29 did not.

Thus, in biliary regurgitation cases there were roughly 39 per cent successful recoveries of *Bacillus coli* against 61 per cent failures of recovery. And in all the *Bacillus coli* infections of the 150 cases studied there was regurgitation of bile in, roughly, 49 per cent, and no regurgitation in 51 per cent. Can any one make a deduction, from these figures, relative to the physiology of biliary regurgitations from the bacteriological aspect? Frankly, we cannot, other than it seems that duodenal anastalsis is not necessarily an index of impaired motility in the gut tube beyond.

Again the question of stomach motility was gone into as affecting the duodenal flora, and it was found that the hypermotile cases gave

as many positive cultures as the atonic or hypomotile cases, and the sterile returns were almost equally divided between the two types.

Finally two great secretory classes were investigated:

1. The acid cases which attained at some point in the fractional analysis an arbitrary figure of 50° for free HCl, or over, as well as those which could be designated as of the continuous secretory type wherein the fasting free HCl was found over 25°, and

2. The achylia cases.

Of the former (1) there were 37 cases in 200 studied, or 18.5 per cent. The culture was sterile on one or more occasions in 13 of these 37 cases, or 35 per cent.

Of the achylia group (2) there were 15 cases in 200, or 7.5 per cent. The culture was sterile on one or more occasions in 3 of these cases, or 20 per cent.

There was no dominance of any one type of organism in the achylia cases. The cultural morphological returns ran about the same in these two great secretory classes, aside from the slight tendency toward more sterile returns in the hyperacid class.

It was hoped that a conclusion could be reached by studying those cases showing a continuous secretion. Here was a group of cases in which the gastric acidity is always high; in which the fasting residuum shows as high a free acid or a degree of acidity within a few points of being as high as the terminal high acidity found in these cases; but our hopes were ill founded. We said—if the hydrochloric acid does really protect the individual against infection, why should not a continuous type of secretion do this to a greater extent than any other type of secretion—that is, the intermittent, or so-called normal type, or the type in which the secretion is always low, or, again, the achylia type?

If we can depend upon the results of duodenal culturing in forming an opinion as to the passage of infection through the stomach and its spreading up through the bile tract, providing it be not lymph-borne or blood-borne, why should not these cases of continuous secretion fail, almost invariably, to give positive cultures; why should not these cases of continuous secretion be the ones to give us the great majority of sterile cultural efforts? We believe that the method of taking cultures from the duodenum, through a sterile tube after thoroughly washing the stomach with numerous wash waters, by which that organ is mechanically cleansed rather than chemically sterilized, and that douching the duodenum after the tip has progressed that far, is essentially a surgically clean method, and usually fails to show the ordinary organisms of contamination. Therefore we see no reason why we should not accept the bacteriological findings as correctly interpreting the presence or absence of the organisms that may or may not be infecting the host. But when we came to working out statistics to show this fact, we were

surprised to learn that there was very little difference in the bacteriological findings between the continuous secretory group and the complete achylia group. There were a few more sterile returns, it is true, but not the great preponderance of sterile returns that was expected. Besides, the low acid group and the achylia group, too, were well represented as giving sterile returns.

Here an experiment was made. Cultures were taken of the two types of bile as it was seen flowing through the tube window from patients with high acidity who were being drained by the non-surgical method of Lyon. There was to be seen, perhaps, a clear bile, but always a creamy bile passed by and was perhaps the only one observed in a highly acid case. We have shown that this creamy bile is produced by the hydrochloric acid precipitating fats and other as yet unknown substances from the bile, and possibly, too, from the pancreatic juice. However, the point is this—creamy bile means the admixture of gastric juice and bile. Now, if we try to make a culture of this bile, we shall very likely find that no growth will result, whereas the clear bile that may be found flowing an instant later, will show one or more infecting organisms. This, then, seems to be one point in favor of the gastric juice acting as a germicide—a mildly acting one it may be—but sufficiently strong to prevent the growth of the organisms in our culture medium if intimately mixed with these organisms, as they are being planted. It seems to be, as well, one point in favor of the bile being the medium carrying the infecting organisms.

The question as to what is infected—the bile, the duodenal contents, the stomach contents, or the tube—is a difficult one to answer to the satisfaction of every one. From our observations, however, we feel fairly well convinced that the bile carries the various organisms which we usually recover in the culture. We do not know that any one can definitely answer this question, but in those cases in which repeated cultures are made, the same organisms will very often be picked up time and time again. It must be remembered, however, that many patients are infected with several types of bacteria at one time, and that when the cultural reports do not agree, it does not mean that either of the bacteriological examinations is wrong. The first culture may show streptococci; the second may show staphylococci; or *Bacillus coli* may be the only organism recovered, even though others may be present and not found, because of the extremely rapid growth of this organism obscuring the more weakly growing bacteria. We have in mind a case which had nineteen cultures taken during the two years that he was under observation. The first culture gave *Bacillus coli* in pure culture. The second, taken five days later, gave *Staphylococcus aureus*. A third culture, two weeks later, gave *Streptococcus hemolyticus* and *Staphylococcus aureus*. There is no question in our minds that these were all there originally, but the rapidly

growing *Bacillus coli* obscured the others in the first culture, and it was only on the third attempt that the streptococcus, which is difficult to grow, was found. The case just referred to is of interest, too, because it showed the improvement in the cultural findings that can be brought about by the use of vaccines. The streptococci did not appear after six months' use of an autogenous vaccine. The staphylococci were more resistant; and *Bacilli coli* were the last to go. And we do not believe that *Bacillus coli* had gone forever, for we have seldom seen *Bacillus coli* completely removed by the use of vaccines. In this case, however, the last three cultures, taken over a period of three months, were invariably sterile.

Now let us pass on to the experiments which were made.

Experiments. The stomach content was withdrawn under the usual aseptic method which is followed in preparing a patient for biliary culture. The fluid was placed in a sterile bottle and sent to the laboratory. A time interval of from one to three hours elapsed from the hour of extraction until the experiments were started. In all 26 stomach specimens, (fasting or digesting contents and wash waters) were examined, according to the technic which follows this paragraph. Inasmuch as we were anxious to know what element of the gastric juice is responsible for its bactericidal action, it was thought wise to check our experiments with an artificial juice containing no pepsin, organic acids, acid phosphates, or combined hydrochloric acid. We would use a solution of hydrochloric acid in distilled water and see how closely it would parallel the results obtained with the natural gastric juice, at various degrees of free hydrochloric acidity. Our important question was—what effect will gastric juice of various degrees of acidity have upon those organisms commonly found in bile cultures, such as staphylococcus, streptococcus and *Bacillus coli*; and at what interval of time exposure will the bactericidal action be manifested? There were two other questions that we desired to answer while our investigations were being carried on. The first was—what will the bacteriological examination of these stomach extractions reveal? And, last—what effect will these gastric juices of various degrees of acidity have on *Bacillus acidophilus*? The tables (II, III, IV) which we have prepared from the information obtained by these experiments, give in detail the results of our efforts to answer these questions.

Technic used in Determining the Sterility and Germicidal Activity of Gastric Juice. *Bacteriological Examination.* Immediately upon receipt at the Institute, 1 cc of the gastric juice was cultured in 0.2 per cent glucose hormone broth; 2 or 3 drops were spread over a human blood hormone agar plate, and incubated for forty-eight hours at 38° C. Smears were made of the bouillon cultures and the colonies fished from the blood plates. Each microorganism isolated was subjected to the various identifying tests.

[illegible]

TABLE III.—EFFECTS OF SOLUTIONS OF HCL EQUIVALENT TO THE VARIOUS DEGREES STUDIED IN GASTRIC JUICE ON BACTERIA.

Data.	Degree of Acidity.	Streptococci (hours).						Staphylococci (hours).						Bacillus coli (hours).					
		0	1	1	1	1	2	0	1	1	1	1	2	0	1	1	1	2	
HCl in distilled water . .																			
Representing HCl- 10 . .	10	+++++OO	OOOOOOO	OOOOOOO	OOOOOOO	OOOOOOO	OOOOOOO	+++++++	+++++++	+++++++	+++++++	+++++++	+++++OO	OOOOOOO	+	+	+	+++++OO	+
Representing HCl- 20 . .	20																		
Representing HCl- 40 . .	40																		
Representing HCl- 50 . .	50																		
Representing HCl- 80 . .	80																		
Representing HCl-100 . .	100																		
Physiological salt solution control	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE IV.—EFFECTS OF GASTRIC JUICE OF VARIOUS ACIDITY ON BACILLUS ACIDOPHILUS.

Control	Physiological salt solution	0	1	1	1	1	1	1	2										
23	F. 0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
24	T. 10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
26	F. 0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
22	T. 10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
22	F. 10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
25	T. 25	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
20	F. 20	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
21	T. 40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	F. 45	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	T. 80	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	F. 55	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	T. 70	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	F. 90	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	T. 110	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Twenty-four hour growth in whey.
Arranged according to degree of HCl.
Inoculated in physiological salt solution and gastric juice of varying acidities.

Bactericidal Tests. Each gastric juice was centrifugalized at high speed immediately after culturing, and the clear supernatant fluid removed and placed in a sterile bottle. It was then placed in the refrigerator at 6° C. and held until the next morning, when the bactericidal tests were made. Subcultures of the bacteria used in the bactericidal tests were made in 0.2 per cent glucose hormone broth on the day the gastric juices were received and used the next morning in the tests. This made available for use cultures of approximately twenty hours' growth. A series of six sterile test-tubes was used for each gastric juice. In each of three tubes was placed 2 cc of gastric juice, in the remaining three tubes 2 cc of sterile physiological salt solution. To one of the three tubes containing the gastric juice was added 0.2 cc of the twenty-hour broth culture of *Streptococcus viridans*; to the second tube a like amount of *Staphylococcus aureus*; to the third tube the same amount of *Bacillus coli communis* culture. The three tubes each containing 2 cc of physiological salt solution were treated in a similar manner. This gave one tube containing gastric juice with one of the three microorganisms used in the tests in suspension, and one physiological salt solution suspension control of the same microorganisms. These tubes were held in a water bath at 38° C. and cultured as follows: Immediately upon addition of the bacteria to the gastric juice, one-quarter, one-half, three-quarters, one and two hours later. The physiological salt solution control was also cultured at the same time.

Method of Subculture. All subcultures of the gastric juice suspension and control were made in 0.2 per cent glucose hormone broth, with pH 7.2 which was previously tested for its cultural properties for these bacteria. Two loopfuls of a 4 mm. loop were transferred to a tube of the above medium at the stated intervals.

These subcultures were incubated at 38° C. in an incubator for forty-eight hours, when the results were read and interpreted by plus or zero signs. The plus (+) sign indicating growth. The zero (0) sign indicating no growth. The same technic and interpretations of tests were carried out in determining the germicidal properties of the gastric juice for *Bacillus acidophilus*, except that the culture medium used was Cohendy Whey with pH 7.6. This medium gave a most luxuriant growth of this microorganism.

The solution of hydrochloric acid equivalent to the degrees of HCl in the gastric juices tested, was prepared by adding sufficient concentrated hydrochloric acid to sterile distilled water to prepare a normal solution. Further dilutions with distilled water were made from this normal solution, and the degree determined by titration with $\frac{N}{10}$ sodium hydroxid solution. In other words a hydrochloric acid solution of 10 should be neutralized by 10 cc of $\frac{N}{10}$ sodium hydroxid solution.

TABLE V.—RELATION OF INTRAPERITONEAL AND BY MOUTH INFECTIONS IN EXPERIMENTAL ANIMALS.

Microörganism.	Method.	Nature of suspension.	Broth culture, 0.5 cc.	1 tenth cc.	1 hundredth cc.	1 thousandth cc.	1/10 thousandth cc.	1/100 thousandth cc.	1 millioth cc.	1/10 millioth cc.	1/100 millioth cc.	1 billionth cc.	Animals.
Pneumococcus	A	NaCl solution, 0.85 per cent	D 26 hrs. O.K.	D 22 hrs. O.K.	D 26 hrs. O.K.	D 28 hrs. O.K.	D 45 hrs. O.K.	D 45 hrs. O.K.	D 45 hrs. O.K.	D 45 hrs. O.K.	D 45 hrs. O.K.	O.K.	Mice.
Pneumococcus	B	Milk	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	Mice.
Streptococcus	A	NaCl solution, 0.85 per cent	D 22 hrs. O.K.	D 22 hrs. O.K.	D 22 hrs. O.K.	D 22 hrs. O.K.	D 22 hrs. O.K.	D 22 hrs. O.K.	D 22 hrs. O.K.	D 22 hrs. O.K.	D 22 hrs. O.K.	O.K.	Mice.
Streptococcus	B	Milk	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	Mice.
B. anthracis	A	NaCl solution, 0.85 per cent	D 18 hrs.	D 22 hrs.	D 42 hrs.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	Strain of B. anthracis used was of lower virulence than that used in following test, known to be of high virulence.
	B	Milk	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	
B. anthracis	A	NaCl solution, 0.85 per cent	D 18 hrs.	D 28 hrs.	D 57 hrs.	D 74 hrs.	D 74 hrs.	D 57 hrs.	D 57 hrs.	D 129 hrs.	O.K.	O.K.	Mice.
B. anthracis	B	Milk	D 129 hrs. O.K.	D 57 hrs. O.K.	D 57 hrs. O.K.	D 57 hrs. O.K.	D 57 hrs. O.K.	D 57 hrs. O.K.	D 57 hrs. O.K.	D 129 hrs. O.K.	O.K.	O.K.	Mice.
Streptococcus	C	NaCl solution, 0.85 per cent	D 18 hrs.	D 18 hrs.	D 18 hrs.	D 30 hrs.	D 30 hrs.	D 30 hrs.	D 30 hrs.	D 30 hrs.	D 30 hrs.	D 30 hrs.	Rabbits.
Streptococcus	B	Broth culture, 1 cc	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	O.K.	Rabbits.
			2 billion bacteria.		1 billion bacteria.		100,000 bacteria.		1000 bacteria.				
B. tuberculosis, bovine	A	NaCl solution, 0.85 per cent	D 13 days	D 22 days	D 22 days	D 22 days	D 22 days	D 22 days	D 22 days	D 22 days	D 22 days	K 22 days	Guinea-pigs.
	B	Milk	K 22 days*	K 22 days*	K 22 days*	K 22 days*	K 22 days*	K 22 days*	K 22 days*	K 22 days*	K 22 days*	K 22 days*	Guinea-pigs.

* Slight tuberculosis.

A, intraperitoneally; B, by mouth; C, intravenously; D, dead; K, killed; O.K., normal.

The germicidal tests of these solutions for the three microörganisms used were almost identical with those used in the tests with the gastric juice.

What, then, should we expect of the gastric secretion in the way of killing swallowed bacteria? What is the protection it offers to the gut tract beyond? To what extent is it bactericidal? The tables we have presented give the result of many hours of patient work by Dr. Harkins in an endeavor to answer this question to our own satisfaction. In viewing these tables you should keep in mind the fact that all the organisms were naked (using an expression of Dr. Kolmer) that is—they are floating freely in a medium and are being added to gastric juice free of mucus; and are not invested by food particles or even a phagocytic cell wall. You will see that even under these ideal conditions there is a limited bactericidal value in the hydrochloric acid of the gastric juice at the normal levels of acidity. The higher the degree of acidity, the greater its bactericidal power—seems to be the rule. You will see, too, that the morphological element plays a large part in making the various organisms susceptible to the action of the acid. Again it is accepted that certain strains of the various types are more resistant than others, and many of the bacteria that are swallowed may be much more difficult to kill than those with which our experiments were conducted.

We wish here to refer to Table V. It represents the tabulated results of experiments conducted on animals to ascertain the relative resistances to a measured amount of infecting organisms, offered by the gastro-intestinal mode of administration as compared to the intravenous or intraperitoneal administration. Space does not permit of a lengthy discussion of these results, which are offered here only as a preliminary report; but a careful study of the table, using the key found below it, will show to what extent the bactericidal activity of the gastric juice was manifested.

Summary. 1. The study of the bacteriological and germicidal values was made on 26 gastric juices and wash waters of various degrees of acidity, from no free hydrochloric acid to a hydrochloric acid value of 100°.

2. Five gastric juices showed no growth, on original culture while the balance proved to contain a variety of bacteria, many of which are common to the oral cavity.

3. Practically no germicidal activity was demonstrated below a free HCl value of 10°.

4. Gastric juices containing free HCl of 10° to 20° were more germicidal for the *Streptococcus viridans* and *Bacillus coli communis* than for the *Staphylococcus aureus*, which organism, even in the higher degrees of acidity, has considerable resistance.

5. Gastric juice containing free HCl from 20° to 100° had a well marked bactericidal value.

6. With solutions of hydrochloric acid in distilled water the results correlated well with those obtained with the gastric juice of the same degrees of acidity.

7. Gastric juice with free hydrochloric acid between 0° and 90° had no effect on *Bacillus acidophilus* except in two instances; one of 55° and another of 90°. This action was only apparent after exposure for forty-five minutes or longer.

8. It is desired to impress the fact that in these exposures the organisms were naked, and not protected by food material and mucus, as they might have been under natural conditions in the stomach.

9. These results confirm, in general, those of other investigations considering the known fact that different strains of the same organism possess marked differences of resistance.

Conclusions. Thus, it can be reasonably inferred, that there is an actual bactericidal action constantly being exerted by the gastric juice because of its hydrochloric acid content (and perhaps because of some other element, chemical constituent or enzyme). Certainly a solution of inorganic hydrochloric acid is just as potent a germicide as the secreted gastric juice having the same degree of acidity. It can be inferred, also, from this study that while many bacteria are killed in transit through the stomach of a man having a normal amount of hydrochloric acid in the gastric juice, many, perhaps very many of the more resistant types, when clothed about with food particles and mucus, pass through unaffected by Nature's barrier.

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ON PANCREATIC CYSTS.

BY MAX EINHORN, M.D.,

NEW YORK.

(From the Lenox Hill Hospital.)

AMONG the diseases of the pancreas the cysts play an important role. They are frequently recognized, either before or at operations, and by the help of surgery can usually be successfully treated. Inasmuch as cysts of the pancreas are quite rare, a report of two cases observed by me, preceded by a few data from the old and recent literature, may not be superfluous.

N. Bozeman,¹ in 1881, was the first to operate successfully upon a patient with a pancreatic cyst. The patient, a woman, aged forty-one years, had had an attack of pains seven years before in the right iliac region. Five years before the abdomen began to enlarge, slowly at first, but gradually increasing in size upon the left side. Seven months before the tumor began to grow rapidly and filled out the entire abdomen. At the same time there was considerable loss in flesh. Bozeman, Thomas and Emmet diagnosed ovarian cyst. During the operation Bozeman made the correct diagnosis. He found the uterus and ovaries normal and traced the pedicle of the cyst to the tail of the pancreas. Ten quarts of fluid were drained off by tapping, and the whole cyst removed by excision. The histology of this cyst was described by H. J. Garrigues.² In the discussion of Bozeman's case before the New York Pathological Society on December 14, 1881, Dr. Peabody³ mentioned that he and Dr. Janeway had presented to the Society in January, 1879, a large cyst of the pancreas discovered at an autopsy. There was half a pailful of fluid in the peritoneal cavity containing brownish flakes. A number of calculi were found, and the walls of the cyst were made up of connective tissue lined with cylindrical epithelium, just as described by Dr. Garrigues.

Gussenbauer⁴ operated upon a pancreatic cyst by attaching same to the abdominal wall and draining it. In his case the ailment was thought to have developed after overloading the stomach. The patient, aged forty years, had partaken, at a banquet, of 7 liters of stale beer and eaten 2 sausages. He was seized with abdominal pains and vomiting. The day following the patient did not feel exactly right, but could resume his usual occupation. Two weeks later, however, the patient noticed a swelling in his gastric region, which began to increase in size during the next fortnight. He lost his appetite and felt full after meals. A month later he began to vomit; lost in weight and suffered greatly from abdominal pains. Two months after the onset of the disease Gussenbauer excised and emptied the cyst; 1900 cc of a bloody fluid were emptied. The fluid

was alkaline and contained the pancreatic ferments. The patient recovered.

Wolff⁵ reports 3 cases of pancreatic cysts. The diagnosis is always difficult. The examination of the stool and urine is usually negative, because in these cases there is enough healthy tissue of the pancreas left to perform all the necessary functions. In 1 case of multiple cysts of the pancreas, the cysts and two-thirds of the pancreas were excised. The patient recovered and regained normal pancreatic functions. In the second case the pancreatic cyst had assumed the size of a child's head and the walls were calcareous. Excision proved to be impossible; suture and drainage was applied. The third case was a pseudocyst, formed after a long standing necrosis of the pancreas, filling out the bursa omentalis and containing 2 liters of exudation. The bursa was opened by severing the *ligamentum gastrocolicum* and the cyst drained. All 3 patients recovered.

According to Heiberg⁶ in one-third of all cases of pancreatic cyst (or pseudocysts) a trauma was the cause of the trouble. Pancreolithiasis also can lead to the formation of a cyst.

Chronic pancreatitis can likewise lead to the formation of pancreatic cysts. As an instance of this type Heiberg cites Körte's case: "A patient, aged forty-seven years, had always been well and had never suffered from any affection of the gall-bladder. On March 26 he became suddenly sick with vomiting and pains in his epigastrium. On April 10 jaundice developed, the feces being clay-colored. The extensive enlargement of the gall-bladder and the history spoke against a biliary calculus. No cachexia; no tumor palpable. On account of the severe symptoms the patient was operated upon July 2. No concrement was discovered, but the head of the pancreas was enlarged, nodulated and hard. A cholecyst-enterostomy was performed. The patient died on July 7. The autopsy showed hemorrhage from the sutured wound toward the inside. Pancreas enlarged, hard. The cross-section showed dilatation of the pancreatic duct. Small cyst degeneration of the head. Compression of the common duct near Vater's papilla."

A good instance of pancreatic cyst after trauma is reported by Hall.⁷ Patient, aged twenty-one years, felt something tear in his abdomen when lifting a heavy load. He was sick and felt faint for a few minutes, but soon recovered and was able to work. A few days later he was seized with severe abdominal colic, requiring large doses of morphin; these attacks recurred at intervals. Five weeks after the onset of the disease the patient noticed a tumor a little to the left of the midline under the border of the ribs. The tumor gradually increased in size while the appetite failed. Patient lost in strength and weight. Shortly before the operation patient had lost 99 pounds and the tumor occupied almost the entire abdominal cavity. "With the great loss of flesh and the enormous tumor in his abdomen, the complaints of the patient of the great suffering

made a pitiable picture long to be remembered. He said that the sensation to him was that the tumor was likely to burst." The patient was operated upon by Dr. Hall and an immense pancreatic cyst was found, containing 23 pints of dark, almost chocolate-colored, thick heavy fluid, which upon analysis proved to be pancreatic fluid. Seventeen and a half days after the operation the patient died from exhaustion.

"The fact that bile regurgitated through the pancreatic duct six days after the operation demonstrated that the duct was not obstructed by a calculus; therefore we reason that if he could have been operated upon early and recovered from the operation, he might have had enough of the gland remaining to sustain life."

H. A. H. Bouman⁸ reports a case of pancreatic cyst which had developed after a trauma—fall from a bicycle. The cyst was of grapefruit size and contained a bloody fluid with all the pancreatic ferments. Bouman succeeded in extirpating the cyst, and the patient made an uneventful recovery. An extensive review of the literature on pancreatic cysts can be found in Bouman's excellent article.

Regarding the non-importance of the pancreatic ferments for the diagnosis of pancreatic cyst, Opie⁹ agrees with Heiberg and Lazarus.¹⁰ Opie says: "The presence in cystic contents of one or more enzymes resembling those of the pancreas was formerly believed to give proof that a cyst had its origin in the pancreas. Not infrequently one or perhaps all of these enzymes are absent in the contents of a pancreatic cyst, whereas fat-splitting, diastatic or proteolytic, enzymes are found in fluids not derived from the pancreas."

In a number of cases of pancreatic cysts, the ferments (amylase, steapsin, trypsin) were found absent.

Thus Primrose¹¹ reports a case of pancreatic cyst which he removed six weeks after a confinement. The patient had no symptoms excepting that a large tumor filled her abdomen. This was believed to be an ovarian tumor. The operation, however, showed that there was a pancreatic cyst. Primrose succeeded in extirpating this large cyst, which he found had no connection with the ovaries but with the tail of the pancreas. In the cyst fluid all the ferments were absent. As to the relations established when the cyst enlarges, Primrose states that occasionally it comes forward between the liver and stomach; it may push the stomach immediately in front of it; it may come between the stomach and the transverse colon; it has been found between the two leaves of the transverse mesocolon; or again it may pass out below the transverse colon.

Of the newer literature we mention but a few articles. Eha¹² described a congenital pancreatic cyst in a child, aged five months. A tumor of orange size was discovered in the left hypochondrium. At operation the mass was found to be a cyst attached to the tail of the pancreas by a broad base. The cyst was dissected, the pan-

creatic portion transfixed, and the abdomen closed. The child made a rapid recovery and remained well.

The case of Bellini and Salzstein¹³—a pancreatic cyst developing after a cholecystectomy—resembles one of my own cases (A. H.). Bellini and Salzstein's case is as follows: A man, aged forty-six years, had several attacks of biliary colic. A gangrenous gall-bladder with stones were removed by operation. Two and a half, and four weeks after operation there were two attacks of colic radiating down the left anterior abdomen to the iliac region. Shortly afterward development of epigastric tumor, increasing in size and requiring operation two and a half months later. A pancreatic cyst was found containing 4 quarts of brownish fluid, with pancreatic ferments and bile. They say: "Perhaps the conclusion is justified that in cases of pancreatitis complicating gall-bladder disease, especially if there is pronounced infection, one of two methods should be followed: (a) cholecystostomy with drainage for several weeks; or (b) cholecystectomy with additional drainage of the common duct."

In some instances of pancreatic cysts the symptoms are very mild. Thus Marogna¹⁴ reports a case of pancreatic cyst in a man, aged twenty-three years. The symptoms were a feeling of fulness in the upper abdomen, without any disturbance of digestion. The examination revealed a somewhat fluctuating tumor above the navel, extending to the left costal margin. In the urine and feces nothing abnormal was found. The operation revealed a cyst connected with the tail of the pancreas, containing 2 quarts of a brownish fluid. Drainage cured the patient in two months. Drainage seems to be the operation usually performed on account of the smaller percentage of mortality.

In some instances the course of the disease is a very protracted one and the loss of weight considerable. Bevan's¹⁵ case is as follows: The patient, aged fifty-five years, was troubled for several years with a gradual loss of weight and a steadily increasing tumor of the abdomen. At the time of operation, the patient had lost 50 pounds in weight, while the tumor had filled almost the entire abdomen. At the operation the tumor was found to be a cyst of the pancreas containing over 2 gallons of a dark fluid with some grayish debris. Resection was impossible, so the cyst was attached to the abdominal wall and drained. Patient made a good recovery.

An excellent example of Nature's power to heal very severe, almost fatal, complications in pancreatic cysts is given by McWilliams:¹⁶ The patient, a female, about sixty-two years of age, had been operated upon by this eminent surgeon in 1910 for a pancreatic cyst. Previous to operation the patient had been suffering from periodic attacks of pain in the left upper quadrant requiring morphin. At the time of operation there was a large transverse indistinct soft mass, not nodular, smooth, lying 4 inches below the

ensiform process. The feces contained occult blood, but no pus or red cells, or any excess of fat. A cyst, the size of a large grapefruit, was discovered at laparotomy. The needle had been inserted through the gastrohepatic omentum. After withdrawal of the needle the wall of the cyst was drawn up to the abdominal opening and a trocar and cannula were inserted, evacuating over a quart of fluid. Steapsin and trypsin ferments were found present in the fluid. A year later the patient returned with a tumor on the left side of the abdomen. An operation revealed that the cyst had filled up again. A large amount of chocolate-colored fluid was evacuated. Excision was impossible. The cavity was swabbed out with iodine solution and a drainage tube inserted. The edges of the cyst were sutured to the abdominal wound edges. For one year the patient wore the drainage tube and felt well. Then she began to complain of colicky pains. The discharge from the drainage tube increased in amount and became greenish-yellow and macerated the skin. At the same time it was noticed that food passed out from the sinus. It was assumed that the cyst wall had perforated into the duodenum. An operation was considered inadvisable. Patient got along fairly well for nine months when epigastric pains reappeared. A diagnosis of cholecystitis was made, but patient refused an operation at that time. Three months later the sinus healed completely and did not reopen afterward. About nine months later the patient was seized with agonizing colicky epigastric pain with fever, and was operated upon at the Paterson Hospital by Dr. Maclay, who removed the gall-bladder containing 54 stones. The patient has remained well ever since.

As seen from the above literature, trauma and pancreatitis form the main causes for the development of pancreatic cysts. In my own two cases which came to operation, pancreatitis was the etiological factor for the origin of the cysts.

Case Reports. CASE I.—A. H., aged forty-seven years, consulted me on August 31, 1918. He gave a history of several severe attacks of biliary colic requiring hypodermics of morphine. A few days ago, after a violent attack of upper abdominal pain, principally on the right side, the patient developed jaundice. On September 4, 1918, the patient entered the Lenox Hill Hospital. He was deeply jaundiced. On palpation a resistance could be made out distinctly under the liver, which was ascribed to a filled gall-bladder. The gastric contents showed a total acidity of 70. The duodenal contents bloody; no bile; amylase, 1; steapsin, 0; trypsin, 0. The diagnosis was cholelithiasis with obstruction of the common duct.

September 10 the patient was operated upon by Dr. F. Torek. Several gall stones were found in the common duct and one big one was lying within and occluding the cysticus. The gall-bladder

of large size (10 cm. long), thickened and reddened, contained a watery mucous fluid without bile. A cholecystectomy was done and the patient progressed fairly well for twelve days. On September 23, however, patient was seized with violent persistent vomiting and fell into a profound collapse. Atropin was given in large doses and on September 25 the duodenal tube was introduced. The next day (September 26) the tube had reached the duodenum and ali-

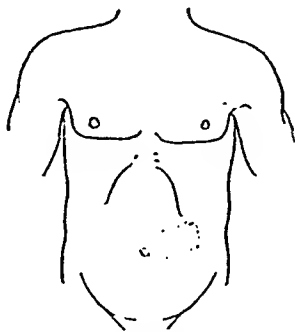


FIG. 1.—A. H., October 30, 1918.

mentation by this route was established. Patient picked up and stood the nourishment well. On October 4 the tube was withdrawn and nourishment by mouth resumed. On October 14 the patient left the hospital feeling quite well. On October 30 a mass was discovered in the left lumbar region (Fig. 1). The tumor did not appear to have any connection with the spleen, and it was questionable whether it belonged to the pancreas or left kidney. The urine was free from albumin or sugar and in this way showed that the

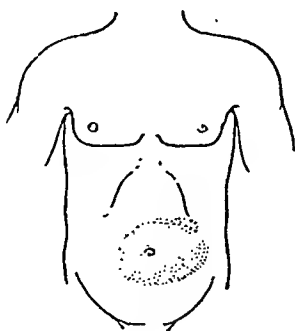


FIG. 2.—A. H., November 11, 1918.

kidneys were not markedly diseased. The patient had been treated meanwhile by another physician for a splenic tumor by application of roentgen-rays without any improvement, the tumor growing bigger all the time. On November 10, when the patient returned to the hospital, I found an extensive tumor occupying two-thirds of the abdominal cavity, starting from the left side and spreading over to the right mamillary line. (Fig. 2.) There was fluctuation

present, and a diagnosis of a probable pancreatic cyst was made. An operation was recommended. November 12 patient was operated upon by Dr. F. Torek. A big cyst connected with the pancreas was found. About 3 quarts of a dirty looking bloody fluid was aspirated out of the cyst and then drained. The fluid contained no pancreatic ferments, but there were found pus corpuscles, hematin and fatty acid crystals. The patient recovered without fever (highest temperature 100° F.) and was discharged from the hospital on December 8, 1918.

The patient presented himself on March 2, 1924, and reported that he had had no trouble after the operation, having gained about 40 to 50 pounds, and having since enjoyed perfect health.

CASE II.—B. D., married, aged forty-six years, stated that in July, 1923, he was seized with burning pains in the epigastrium. His father had died of carcinoma; his family history was otherwise negative. He consulted his family physician, who gave him tem-

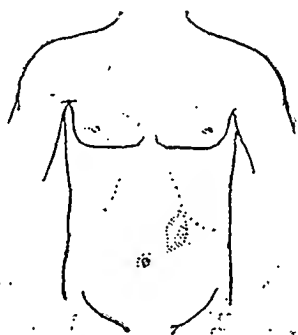


FIG. 3.—B. D.

porary relief for a while. But the patient drank heavily for about four weeks and the pains returned; but they were now located in the back of both shoulders, moving from right to left. The pains continued until August 24, when he was seized with an attack of vomiting that continued off and on for thirty hours. He had lost almost 30 pounds in weight in the last three months.

The patient came under my care on August 30, 1923. The physical findings at that time were as follows: A resistance could be felt beneath the left margin of the ribs, corresponding to the size of a fist. No nodules could be palpated, but at times fluctuation could be elicited in this area. (Fig. 3.) The tumor was situated beneath the left costal margin and was frequently visible to the eye as a bulging out body lying apparently over the stomach. At times however, the mass was not visible but could be detected by palpation. The liver was enlarged.

The roentgen-ray report (September 1, 1923), was as follows: "There is a marked defect involving the major part of the greater

curvature. (Fig. 4.) The duodenal cap is dilated and held firmly toward the liver. The cecum is filled with some irregularities at the lower pole. Stereoroentgenograms reveal a distinct pressure defect involving the distal transverse and splenic flexure.

"The above findings indicate a tumor mass causing a pressure defect on the greater curvature of the stomach. This I believe due to either a cyst of the pancreas or a tumor of the left kidney." (Dr. Priest.)

Urine: Specific gravity, 1024; albumin, 2+; leukocytes, epithelial cells, hyalin and granular casts. There was no fever on admission, and the temperature remained normal until operation.

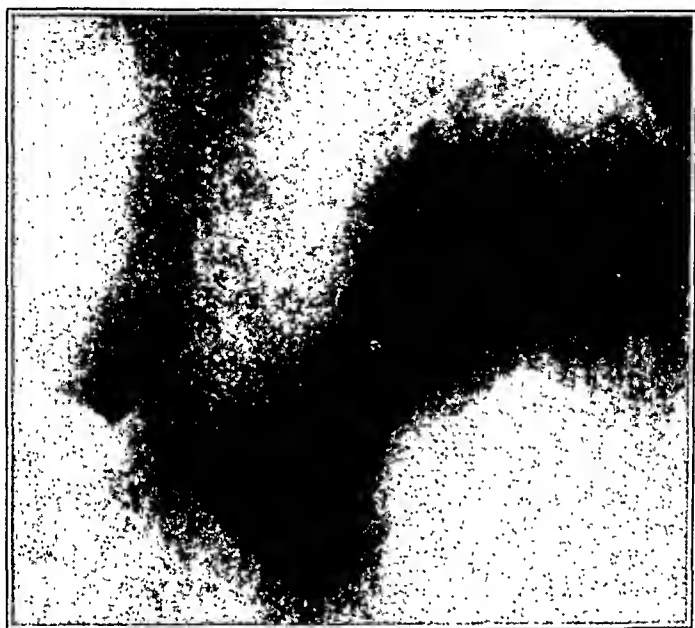


FIG. 4.—Roentgen-ray photograph of stomach of B. D. after barium. Defect seen on greater curvature, caused by pressure of the pancreatic cyst.

Duodenal contents were light greenish-yellow, turbid, alkaline (20), and contained calcium, bilirubin and cholesterol crystals and mucus. (A, 6; S, 1; T, 1.) The digestive test capsule showed remaining after seventeen hours: potato, fat; thymus (no nuclei).

Blood count: Hemoglobin, 70 per cent; erythrocytes, 5,640,000; leukocytes, 10,000, of which 5570 were polymorphonuclears and 4570 lymphocytes.

Gastric contents showed free hydrochloric acid, 46; total acidity, 60. The test for blood was negative.

A diagnosis of pancreatic tumor or cyst was made, and the patient was operated upon September 6, 1923, by Dr. H. Fischer. A pancreatic cyst was found, extending from the tail of the pancreas. The cyst was emptied, sutured to the abdominal wall and drained.

Examination of contents of cyst: Specific gravity, 1021, reaction, neutral; a trace of bile, blood test positive; urobilinogen, negative;

albumin, large amount present; protein, 3.170; sugar, 0.75 per cent (fermentation method); (A, 3; S, 0; T, 0); (cholesterin crystals, leukocytes, erythrocytes and mucus).

The patient made an even recovery and left the hospital on October 1 with a considerable gain in weight and enjoying good health.

Remarks. In the two cases just described, pancreatitis seems to have been the cause for the development of the cyst. In Case I, the patient (A. H.) had a collapse with persistent vomiting about twelve days after his operation for a calculus in the common duct, a condition favorable for pancreatic disease.

In Case II, the patient (B. D.) had a somewhat enlarged liver and used alcoholic beverages at times excessively. An alcoholic gastritis most probably gave rise to a pancreatitis which laid the foundation for the cyst.

Summary. 1. The most prominent symptoms in cases of pancreatic cysts are fulness after meals, gastric distress and vomiting at times. The larger the cyst the more distress is present.

2. The diagnosis of pancreatic cyst is not difficult, provided the cyst has assumed considerable proportions and the clinician is aware of such a possibility. The marked features which help to recognize this disease are the following:

A. There is a tumor usually in the left hypochondrium with a smooth even surface, frequently showing fluctuation.

B. The principal protrusion appears to lie in the left nipple line beneath the costal margin. The dulness produced by the mass on percussion does not extend to the spleen on the left side, nor to the liver on the right.

C. Changes in the configuration of the tumor are of frequent occurrence, dependent upon the state of the stomach (whether the latter be filled or empty).

D. There is a filling defect in the stomach due to pressure from the outside (recognizable by roentgen-rays).

E. Either a very rapid increase in the size of the tumor (within a month or two), or on the other hand a very slow protracted course (several years) is characteristic for a cyst.

3. In regard to treatment, there is only one course to pursue, and that is to operate as soon as the diagnosis is reasonably made; for without operation the condition usually leads to protracted illness, great suffering, and death. An operation, however, either removal of the cyst or aspiration and drainage after suturing the opened cyst to the abdominal wall—is ordinarily followed by a permanent cure; this occurred in the two cases described.

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THE STORY OF MAGNESIUM SULPHATE WITH SPECIAL REFERENCE TO ITS USE IN BILIARY DRAINAGE.

BY H. W. SOPER, M.D.,

ST. LOUIS, MO.

Historical Review. The history of this salt presents many interesting angles. Used almost universally by physicians for many years as a purgative, it has recently had a remarkable development due largely to the brilliant work of Meltzer, who possessed the rare quality of mind that enabled him to become an eminent physiologist and a great clinician. All his contributions to physiology had a direct bearing on clinical medicine.

The town of Epsom, 15 miles from London in the county of Surrey, contained a spring which was unnoticed until about the year 1618. It is related that a farmer, named Henry Wicks, attempted to water his thirsty oxen at the spring, but to his surprise the animals would not drink. He tasted the water and found it salty and bitter. The townspeople soon began to use it as a local application in sores and skin affections. Finally Lord Dudley North had the courage to take it internally and was so greatly benefited that the water soon attained considerable fame. He published a pamphlet in 1645 entitled, "The Forest of Varieties," in which he sets forth the virtues of the water.

We are indebted to Prof. R. D. Rudolph¹ in an article in the *Canadian Medical Association Journal* for the early history of Epsom Salt. He cites the book entitled: "The Bitter Cathartic

Salt in the Epsom Water," published in the year 1695 by Dr. Nehemiah Crew, to which he had access in the library of the Royal Society of Medicine.

Epsom was soon a fashionable resort and society flocked there for the "cure." It was recommended for every known disease. Its popularity as a resort waned soon after the famous Dr. Richard Russell in the year 1753 introduced sea bathing as a remedy. The spring is still in existence but the waters are no longer used medicinally.

The use of magnesium sulphate as a purgative was soon world wide. In 1834 James Henry² reviewed the literature and advised the addition of dilute sulphuric acid to improve the taste. At that time the famous "Black Draught," consisting of an infusion of senna holding in suspension a mixture of magnesium and sodium sulphate was used in the hospitals and institutions. In 1866 H. R. DeRicci³ reported the value of magnesium sulphate in the zymotic diseases, especially yellow fever. In 1900 Dr. N. F. Howard⁴ in his paper entitled: "Magnesium Sulphate as a Potent Remedy," summarizes the indications for its local medicinal use as follows: (1) Scalds and burns, (2) the stings of insects, (3) bruises, contusions and lacerations, (4) joint sprains, (5) erysipelas, (6) dry salt for scalp eruptions.

Howard contrasts the opinion in regard to its use internally at that period and fifty years ago; he remarks that fifty years ago one would have been liable to suit for malpractice for using it in a case of puerperal septicemia, while in this era, failure to use it would meet with severe censure.

In 1899 F. A. Rouget⁵ extolled its use in the treatment of dysentery. The use of the salt about this period may be summarized by a quotation from *Foster's*⁶ *Therapeutics*:

"Magnesium sulphate or Epsom salt is a cathartic which acts promptly without giving rise to nausea or griping, produces watery stools and is rarely rejected by a sensitive stomach. It is a most useful cathartic in febrile states, colic and other conditions when a full movement of the bowels without any secondary depressing effects is desired. In the early stages of dysentery, before there are very marked changes in the intestinal mucous membrane, there is scarcely any remedy of equal value: Two-dram dose in a wine glass of water with a few drops of dilute sulphuric acid is given every hour until complete evacuation of fecal matter has taken place. The average cathartic dose is 1 ounce taken on fasting stomach."

It was largely used in acute abdominal "inflammations." I recall the lectures of the famous surgeon, Dr. E. H. Gregory in the St. Louis Medical College in 1894, who admonished his students, "For Heaven's sake do not cut a belly open without at first giving small doses of Epsom salts a trial."

In 1894 Wade⁷ as well as Fincke⁸ experimented in the use of the salt as a purgative by hypodermic administration. Both authors decided that it occasionally produced catharsis but was unreliable. In 1895 James H. Wood⁹ concluded that the salt hypodermically produced paralysis of the inhibitory action of the nerves of the superior mesenteric plexus and thus allows free flow of liquid from the intestinal glands. The same effects are produced by large doses given by mouth.

That the drug is not without toxic effects is evidenced by the following reports in the literature: In 1891 Dr. Wm. Sang¹⁰ in the *Lancet* reported the death of a woman who had taken 4 ounces of magnesium sulphate. He pointed to other cases and said that Taylor's work on poisons records the trial of two men in 1844 at Huntingdon who were found guilty of feloniously killing another man by administering large quantities of Epsom salts in his beer. Dr. J. Headley Neele,¹¹ in 1896, reported a case of poisoning in a fifteen year old boy, who had taken 2 ounces of the salt without purgation. Charles Frazier,¹² in 1909, reported in the *Lancet* 6 cases in which the administration of magnesium sulphate was followed by untoward symptoms, 5 of which terminated in death. James P. Prestley¹³ reported poisonous effects following 2 teaspoonfuls of magnesium sulphate. Three weeks later the same dosage produced the same symptoms. (This was evidently a case of sensitization.) Wm. F. Boos¹⁴ reported 10 cases of magnesium sulphate poisoning following administration of the drug by mouth. Dr. Wm. W. Anderson¹⁵ reported 2 cases of magnesium sulphate poisoning in children with recovery. Investigation of these 2 cases showed that the children received 2 ounces of the drug, which was given in the evening, followed in the morning by a dose of thymol. One and one-half ounces of magnesium sulphate were again given at noon—an entirely unwarranted dosage.

The epoch-making work of Meltzer,¹⁶ which appeared in 1905, was entitled: "Inhibitory and Anesthetic Properties of Magnesium Sulphate." Experiments on animals proved that intravenous injections of small doses inhibit the respiration and finally cause paralysis of the entire body. Local applications to nerve trunks block conductivity and abolish excitability of the nerves. Subcutaneous injections produce deep narcosis with complete muscular relaxation. Subarachnoidal injections produce immediate anesthesia and paralysis of the posterior extremities. All these inhibitory and anesthetic phenomena may completely disappear again. In 1906 Meltzer and Haubold¹⁷ repeated the animal experiments on human beings with similar results. They advise the dosage of 1 cc of 25 per cent solution to 1 kilogram of body weight. The above work formed the basis for the use of magnesium sulphate in the treatment of tetanus forming one of the most interesting chapters in the history of medicine. Blake, in the Roosevelt Hospital,

New York, appears to be the first one to use it in the treatment of tetanus. Favorable reports soon appeared in the world's medical literature: In America by C. J. Holman,¹⁹ George Parker²⁰ and others; in Germany, by Kocher,²¹ Stadler,²² Weinbrand and Unger²³ and many others, in Great Britain, by N. Markwell,²⁴ O. Smithson²⁵ and M. C. Gardner.²⁶ In 1916, Meltzer¹⁸ summarized the treatment in a masterly article. The treatment of tetanus by means of magnesium sulphate is now firmly established. The subcutaneous method is growing in the favor as evidenced by recent reports of Parker (*loc cit.*) H. Stadler (*loc cit.*) and Carroll Smith.²⁷

The use of the drug in surgical anesthesia was first advised by Meltzer and Auer.²⁸ It was used in man as an anesthetic by Chas. H. Peck and Meltzer,²⁹ who concluded that the employment of the salt may prove to be a practical and advantageous method, because it will produce simultaneously a moderate degree of relaxation of the muscular mechanism and because untoward effects can be rapidly reversed by the administration of a solution of calcium chloride. They believe however that it should not in the present state of our knowledge be used generally. Arthur H. Curtis³⁰ reports a fatal case in which magnesium sulphate was used as an aid in anesthesia and concluded that it is not safe for general use.

The fundamental work of Meltzer and the brilliant success of the salt in tetanus caused the drug to be used in a large variety of cases. Schroeder³¹ reports 9 cases of chorea minor in children and 2 cases in adults rebellious to all other measures, but yielding to a 20 per cent solution of magnesium sulphate in small slowly increased doses of from 0.2 gm. to 3 gm. a day. Natali³² as well as Cavalieri³³ reports good results in chorea. In spasmophilia good results are reported by N. Berend,³⁴ Genoese³⁵ used it in whooping-cough without effect. Hansen³⁶ endeavored to establish the positive action of magnesium sulphate against the toxicity of arsenic. It prolonged the average life of a series of 50 rabbits poisoned by arsenic, but cannot be said to have saved life in rabbits. It is well established as an antidote in carbolic acid poisoning. Sajous³⁷ states that the sulphate of sodium or magnesium should be given freely as an antidote as they form insoluble sulphocarbates. In the event the patient survives, the sulphates should be continued for several days in small doses, inasmuch as the soluble sulphates have the quality of penetrating the tissues.

J. J. Hogan³⁸ treated 200 cases of influenzal pneumonia with intravenous magnesium sulphate solutions and calcium chloride solutions with mortality of 16 per cent. He strongly recommends the treatment. Weston and Howard³⁹ used 50 per cent solution of magnesium sulphate in 2 cc doses as a sedative, reporting very good success in 82.7 per cent of the cases. Harrar⁴⁰ reports 9 cases of puerperal streptococcemia with intravenous injections of mag-

nesium sulphate with reduction of the mortality from 93 per cent to 20 per cent.

Infected wounds are reported to be favorably benefited by treatment of magnesium sulphate solutions by Freese⁴¹, Morrison and Tulloch⁴² and others. Guggesberg⁴³ reports 2 cases of eclampsia without benefit. Kirkpatrick⁴⁴ used saturated solution of magnesium sulphate in corneal ulcers with satisfactory results. Meltzer⁴⁵ reaffirms the good results secured in scalds and burns, thus in an interesting manner adding the highest scientific dictum to the findings of the townspeople of Epsom.

Edward A. Leonard, Jr.,⁴⁶ reports 12 cases of delirium tremens in which lumbar puncture was done and various quantities of cerebrospinal fluid were removed according to the amount of pressure found. The amount removed varied from 10 to 40 cc. After removal of the cerebrospinal fluid, 1 cc for every 25 pounds of body weight of a 25 per cent solution of magnesium sulphate, at a temperature ranging between 95° and 100° F., was introduced by means of a syringe through the lumbar puncture needle into the canal. Ten recoveries and two deaths.

Blackfan and Mills⁴⁷ report the influence of magnesium sulphate on blood-pressure in acute nephritis. They observe that there is a lowering of blood-pressure following the administration of magnesium sulphate. When a 2 per cent solution of magnesium sulphate is given intravenously in selected cases, the blood-pressure promptly falls and remains at a low pressure for five hours. The injection is usually followed by diuresis or free catharsis.

In 1915, appeared Meltzer's⁴⁸ article on "The Relation of the Purgative Action of Magnesium Sulphate to Peristalsis and the General Law of Crossed Innervation." The experimental work of Meltzer demonstrated that solutions of magnesium sulphate produced an inhibitory influence upon the peristaltic movements of the intestinal tract of animals whether the salt was given intravenously or applied directly to the mucosa.

In 1918, Soper⁴⁹ published his article on the "Use of Magnesium Sulphate Solutions in the Treatment of Spastic Contractures of the Rectum and Sigmoid Colon." He found it to be of great value in overcoming the spastic contractures of the rectum and lower colon.

Magnesium Sulphate in Biliary Drainage. In 1917 a footnote in Meltzer's⁵⁰ article entitled: "The Disturbance of the Law of Contrary Innervation as a Pathogenetic Factor in the Diseases of the Bile Duets and Gall Bladder," was the inspiration for Lyon's⁵¹ brilliant work in biliary drainage. This work has not only created a tremendous amount of discussion, but has stimulated much investigation of the physiology and pathology of the gall-bladder. Lyon's five reasons for accepting the method were as follows:

1. The law of contrary innervation was correctly applicable to the biliary apparatus.

2. The color and viscosity of the bile obtained in the second aspiration (so-called "B" bile) strongly suggested that it came from its storage chamber within the gall-bladder.

3. The "B" bile from diseased gall-bladder is sometimes thick and tarry, containing mucopurulent flakes, pus cells and bacteria.

4. In cholecystectomized animals, "B" bile is not obtained by any of the aspirations.

5. In patients with gall-bladder disease treated by this method, a marked improvement has been noted.

Einhorn⁵² found that the same kind of bile could be secured from patients in whom the gall-bladder had been removed. Bassler, Luckett and Lutz,⁵³ Dunn and Connell⁵⁴ and others also presented evidence against Lyon's conclusions. Smithies, Karkshner and Oleson,⁵⁵ on the other hand, have defended the Meltzer-Lyon method. Auster and Crohn⁵⁶ in an elaborate work on the physiology of the gall-bladder concluded that the gall-bladder is not an actively functioning organ. It does not rhythmically fill and empty itself under the stimulus of digestion. They are inclined to the belief that the flow of bile originates in the liver and sweeps down the ducts into the duodenum disregarding in main part the gall-bladder. The outflow from the gall-bladder appears to be in the nature of an overflow incontinence.

Fraser⁵⁷ in an experimental study of the use of magnesium sulphate came to the following conclusions: "The results of our experiments were entirely negative. When magnesium sulphate solution was injected directly into the duodenum of dogs or injected into the circulation there was neither acceleration of the rate of flow of bile nor change in the color. In many instances the rate was even somewhat retarded. When bile was injected into the duodenum there was a definite prompt increase in the flow of bile."

B. L. Knight⁵⁸ proposed the following theory as to the action of magnesium sulphate in non-surgical drainage of the gall-bladder. He ascribes its action to the hygroscopic quality of the drug and believes that when the congestion around the ampulla of Vater is reduced, the occluded duct opens. He gave 10 cc of saturated solution of magnesium sulphate every hour until 5 doses were given. No water or food was given for five hours, after which a dry meal was permitted. He reports very good results therapeutically.

In a recent work on the physiology of the gall-bladder, Diamond⁵⁹ supported in the main Crohn's opinion.

Personal Work. In presenting this work on biliary drainage I wish it distinctly understood that my work applies to the therapeutic use of the salt and not to its diagnostic value. Rather than detracting from the method, I believe that it simplifies the technic and will stimulate a wider use of the drug in gall-bladder conditions.

I was early favorably impressed with the therapeutic value of the method and secured many good results. Soon, however, I

noted that purgation followed the application of the salt to the duodenum and that it was impossible to withdraw more than a portion of the solution after allowing it to remain for three minutes in the gut. I observed that the feces of patients drained in this manner were colored by bile pigment. Therefore, but a portion of the bile that formed was being removed by the duodenal tube. Furthermore, I considered that inasmuch as the bile was a solution from which it was so very difficult to secure cultures, it would probably not be injurious to the intestinal tract. Moreover, it was also an important adjunct to digestion, even if contaminated by infectious elements from a diseased gall-bladder. Therefore the gut was probably a better drainage tube than the duodenal tube.

I modified the method by introducing the duodenal tube at night and giving the magnesium sulphate through it in the morning, at once removing the tube. Active purgation resulted. The stools being as a rule definitely bile colored. I continued to secure good results. One particularly severe case of Weil's disease responded well to it. I was fortunate at this time in observing a series of 12 cases of catarrhal jaundice. All the cases were fed on the same soft bland diet. The first 5 cases were treated as above outlined by means of the duodenal tube. Recovery occurred within the usual ten to twelve days' time. The remaining 7 cases were given a saturated solution of magnesium sulphate by mouth every morning on fasting stomach. The results were identical with the 5 cases in which the duodenal tube was used.

The good results secured in catarrhal jaundice emboldened me to continue its use by mouth in all sorts of gall-bladder and duct conditions. My results were as good, if not better, than they had been by the use of the duodenal tube.

The method of administration of the drug varies according to the reaction experienced by the patient. As a rule we give it in daily doses on fasting stomach for a period of one week or more. The dosage varies from $\frac{1}{2}$ to 2 ounces of the saturated solution.* In some cases the continuance of small daily doses, not enough for purgative action, seems advisable. In this connection I was interested in looking over a number of case records in which old ladies attribute their freedom from further gall-bladder attacks to the habit of taking a small dose of Epsom salts every morning, a prescription that was very much in vogue during the nineteenth century.

Here I wish to emphasize that while we are enthusiastic in the treatment of gall-bladder conditions by means of magnesium sulphate solutions we do not regard it as curative. It may shorten the course of catarrhal jaundice and Weil's disease and may be of great benefit in partial inflammatory obstructions of the common

* To disguise the taste we are in the habit of adding 1 dram of compound tincture of cardamom to 1 ounce of the saturated solution. A little cracked ice may be added.

duct and in postoperative contractures of the common duct which frequently follow cholecystectomy, and in other conditions in which for one reason or other surgical operation is contraindicated or postponed. But we still entertain the conception that gall bladder disease requires surgical interference, and when such a diagnosis is established, it is the duty of the internist to advise surgery. It is a matter of common observance that gall bladder disease is subject to remissions and exacerbations, regardless of the form of treatment instituted. Therefore it is obvious that all medicinal therapy in gall-bladder disease must, in the last analysis, form *clinical impressions* rather than *concrete opinions*. We have used the method in over 300 cases and are very favorably impressed with the results.

I attempted to ascertain whether any chemical change occurred in the solution if given by mouth or by duodenal tube. The problem was submitted to the chemical department of Washington University. The following communication by Dr. A. P. Briggs answers the question: "The more I think about this problem the more I feel that there is very little which can be shown by chemical analysis. Conditions as I see them are something like this—Magnesium sulphate is certainly unchanged in passing through the stomach, unless perhaps in concentration; it may be diluted, of course, depending on the amount of fluid in the stomach, but HCl has no action on magnesium sulphate. The presence of hydrochloric acid from the stomach or of sodium bicarbonate from the pancreas may possibly have some influence on the action of magnesium sulphate in the duodenum but this cannot be determined by chemical analysis."

Magnesium sulphate given by mouth will produce the same flow of bile as when introduced directly through the duodenal tube, as may be ascertained by the following simple experiment: Pass a duodenal tube into the duodenum and give the magnesium sulphate through the tube according to Lyon's⁶⁰ technic. The following day use the same technic on the same patient (with the tube in the duodenum), except that the magnesium sulphate solution is given by mouth. The specimens of bile secured will be practically identical in both instances.

As to the action of magnesium sulphate in the intestinal tract, there has been considerable confusion and differences in opinion. Meltzer has been frequently misquoted. It appears that Meltzer did no work whatsoever on the subject of biliary drainage, but merely suggested its use. He states explicitly that sodium sulphate and magnesium sulphate are absorbed from the intestines. He produced toxic effects by injecting it directly into the lumen of the gut. On the other hand Goldschmidt and Dayton⁶¹ in a series of elaborate experiments on animals conclude that the colon behaves toward solutions of sodium sulphate and magnesium sulphate like a semi-permeable membrane. Water is absorbed from hypotonic

solutions until iso-osmotic with the blood. With hypertonic solutions the volume increases and the concentration decreases until near the blood level. Hence there is free passage of water with no diffusion of sulphate. The failure of absorption of these salts from the colon emphasizes the specific importance of the large intestine in saline catharsis.

Wallace and Cushny⁶² found that solutions of sodium and magnesium sulphate in all concentrations tend to become isotonic with the blood. The sulphates in the small intestine behave in the same manner as described in Goldschmidt and Dayton's work on the colon.

Reach⁶³ conducted a series of experiments on animals and found that a 25 per cent solution of magnesium sulphate applied directly to the duodenal mucosa produced an irregularly intermittent relaxation of the sphincter of the common duct, the bile being expelled in spurts. The solution applied subcutaneously and to different portions of the gut had no effect on the sphincter.

Graham and Cole's⁶⁴ recent work on roentgenological visualization of the gall-bladder is destined to throw new light on its physiology and pathology.

Meltzer always emphasized the role that magnesium sulphate played in stimulating the inhibitory phase of peristalsis. Indeed one of his first experiments showed that peristalsis stopped immediately upon direct application of the drug. He attempted to explain its action as a purgative on the theory that the salt was broken up in its passage through the stomach into sodium sulphate and magnesium carbonate, substances which he found stimulated the contractile phase of peristalsis, while the remaining unconverted magnesium sulphate stimulated the inhibitory phase. No experimental work has as yet substantiated Meltzer's theory.

I would suggest that its action might be explained on the theory of osmosis and hydrostatics, as well as the fact that magnesium sulphate produces an inhibitory effect on the *tonus* of the gut. Meltzer defines *tonus* as follows: "The resultant effect of the antagonistic actions may be manifest at the same place and at the same time. *This is tonus*. The degree and the character of the *tonus* depend upon the preponderance of one or the other factor." According to Meltzer's theory magnesium sulphate would lower the *tonus*, thus producing a dilatation in a given segment of the bowel, that is fugacious in character and is rapidly followed by a contraction of this dilated segment. If we can imagine that each successive segment of the bowel dilates and contracts in this manner it would explain the rush action of a dose of Epsom salts.

Summary. Magnesium sulphate is a most potent and reliable remedy and is used in a long list of diseases. Since its physiological action has been established, it is destined to have a much wider employment in medicine and surgery.

There is no essential difference in the therapeutic effect of magnesium sulphate in biliary drainage, whether it is given by mouth or applied by means of the duodenal tube. No chemical evidence exists to show that there is any difference in the solution when it reaches the duodenum, whether administered by mouth or duodenal tube. Indeed chemical opinion is to the effect that no change occurs in the solution in its passage through the stomach except possibly in concentration.*

* My thanks are due to Drs. L. E. Printy, F. R. Finnigan and L. D. Cassidy for aid in the treatment of cases. I am indebted to Dr. Finnigan and Miss Elsie Olson for help in collecting the literature.

A complete bibliography will be furnished in the author's reprints.

THE RELATION OF CHRONIC FOCI OF INFECTION TO KIDNEY INFECTION.

BY RUSSELL L. HADEN, M.D.,

KANSAS CITY, MO.

(From the Department of Medical Research, Deane Institute, Kansas City, Mo.)

THE subject of pyogenic kidney infection is divided rather logically into the following parts: (1) The mode of infection; (2) the pathological anatomy of the diseased process; (3) the type of infecting organism; and (4) the source of the infection. It is the purpose of this paper to discuss primarily the source of the infecting bacteria, but such necessitates also some consideration of other parts of the subject which bear directly on this question.

There seems to be no need for a discussion of the mode of infection in acute kidney disease. The proof seems absolute that the infection is practically always of hematogenous origin. This conclusion has a most important bearing on the question of the source of the infecting organism.

The pathologic anatomy of the different types of kidney infection which we are accustomed to separate off as clinical entities is not so clearly defined. Certain types of infection have been thought by some workers to be caused characteristically by certain kinds of bacteria. Thus Cabot and Crabtree¹ associate infection by the colon bacillus with localization in the pelvic portion of the kidney, and infection by the staphylococcus and streptococcus with abscesses of the kidney cortex. This conclusion I believe to be wrong. It certainly does not agree with the results obtained by animal experimentation. In the great majority of cases it is impossible to interpret clinical pictures and laboratory findings in terms of pathological anatomy. A statement of Helmholtz is of interest in this con-

nection. He says² "It is clinically impossible to differentiate the different forms of kidney infection involving kidney cortex, pelvis, ureter and bladder."

Perhaps the type of infection concerning which there has been the most serious misconception is so-called "pyelitis." The symptom-complex which this term designates is very commonly met with in medical practice. A proper conception of its nature is very important from the standpoint of the origin of the infecting organism. It is probable that a true pyelitis in the sense of a simple inflammation of the lining of the kidney pelvis, rarely occurs. The clinical picture of chills, fever, pain in the kidney region and pyuria, in the absence of obstruction, is in reality usually a pyelonephritis in which the principal lesion is in the medullary portion of the kidney.

The question as to what organism is the primary invader is as yet unsettled. Cultures of the urine from cases of pyuria shows quite uniformly only the colon bacillus. This almost constant finding has confused the whole subject of acute kidney infection very materially. The presence of the colon bacillus has made it difficult for many to believe that the infection could be blood-borne. Cabot and Crabtree³ recovered the colon bacillus from the blood in a number of cases during the chill incident to the onset of an acute kidney infection. In most of the cases studied, the infection seems to have occurred subsequent to an obstruction in the urinary tract. It is a question whether the findings were not due to direct invasion of the blood by colon bacilli already in the kidney pelvis, since Magoun⁴ has shown that bacteria are capable of being absorbed through the renal pelvis and recovered from the blood stream. The finding of the colon bacillus in the blood is thus no proof of the primary casual relation of this organism to a kidney infection in which there is no obstruction.

It is well known that the colon bacillus is a ready secondary invader in the urinary tract. Le Fur⁵ attempted many years ago to produce cystitis in rabbits by the injection of various organisms. He found that when the colon bacillus was injected it could be recovered in pure culture. On injecting other organisms, however, the colon bacillus was frequently recovered with the organism injected and in some instances was the only organism recovered.

Attempts to produce infection of the kidney by the intravenous injection of colon bacilli recovered from the urine of patients suffering from pyelonephritis have met with little success. Thus Helmholz⁶ found kidney lesions in only 8 of 66 rabbits so injected. The frequent recurrence of pyelitis after treatment by lavage of the kidney pelvis suggests strongly that the primary causative factor is not reached by this form of treatment.

The point should be emphasized that urine cultures are commonly made only by orthodox methods. It is quite probable that the

absence of other organisms is often thus explained. The pyogenic organisms found in areas of chronic infection often cannot be recovered by the usual cultural methods. A case of pyelonephritis which I have studied recently, is of interest in this connection. The urine contained large amounts of pus and cultures on blood-agar plates showed only a pure culture of the colon bacillus. Careful study of the stained smears of the urinary sediment showed a very few Gram positive diplococci in addition to the many Gram negative bacilli. The urine was cultured also in deep tubes of glucose brain broth. Smears from the bottom of the tube twenty-four hours later showed a few diplococci. The supernatant fluid was poured off and sterile broth added for two successive days. After the last incubation smears from the broth showed almost a pure culture of a streptococcus.

One must conclude from the facts mentioned that there is much doubt as to the primary etiological relation of the colon bacillus to acute renal disease. There is much to suggest that the initial kidney damage is due to the streptococcus or staphylococcus. It may perhaps be continued by the colon bacillus.

It is probable that with infection present anywhere in the body bacteria are continually entering the blood stream and being excreted by the kidneys. The common occurrence of typhoid bacilli in the urine of patients suffering from typhoid fever is a classic example. Usually, however, the bacteria are excreted without producing evidence of kidney injury. It is well known, however, that acute renal disease may occur during the course of an acute infection located anywhere in the body. Thus multiple cortical abscesses of the kidney are not uncommon with acute osteomyelitis.

The possible relation of chronic focal infection to kidney disease has been considered only recently. The kidney disease produced by bacteria concerned in acute osteomyelitis is due probably to the great virulence of the infecting organism. We know, however, that the organisms in chronic foci of infection are relatively avirulent. If the bacteria from such chronic foci do produce kidney disease as they pass through it must be due to some special affinity of the bacteria for kidney tissue or a selective localization in the sense of Rosenow.

To test experimentally such an hypothesis Bumpus and Meisser⁷ have recently studied a series of cases of pyelonephritis to decide whether the bacteria recovered from foci of infection tend to localize in the kidney of rabbits on intravenous injection. They found that a very large percentage of the rabbits injected with bacteria recovered from chronic foci in such patients had kidney lesions while only a small number of the animals injected with bacteria from patients who were not so afflicted showed kidney localization. The organisms injected were streptococci, obtained in most instances

from dental infection. This idea that kidney infection is frequently produced by the bacteria brought to the kidney from areas of chronic infection in which an especial affinity for kidney tissue has been attained has thrown much light on the source of acute kidney infection and is reflected in different and more thorough methods of treatment. Bumpus and Meisser conclude that pyelonephritis is



FIG. 1.—Culture of a streptococcus from infected root tip in glucose-brain-broth agar. There are very few colonies at the bottom and at the top of the tube, the maximum growth being confined to the middle zone.

usually due to the streptococcus or staphylococcus with the colon bacillus as only a secondary invader. They found quite often that during the acute exacerbation following the removal of the focus streptococci as well as colon bacilli were present in the urine.

My contribution to the subject concerns primarily the study of kidney lesions developing in rabbits as a result of the intravenous injections of bacteria, usually streptococci, recovered from peri-

apical dental infection. I have also studied certain cases of pyelonephritis to determine whether the condition from which the patient suffered could be reproduced in animals with the bacteria isolated from foci of chronic infection.

The material in every case has been cultured in deep tubes of glucose brain broth and glucose brain broth agar (Fig. 1) mediums in which the organisms found in chronic foci grow very luxuriantly and also retain their elective affinity. The details of the technic employed have been described elsewhere.⁸ The organisms recovered have usually been non-hemolytic streptococci. Typical organisms as seen in smears from kidney lesions are shown in Fig. 2.

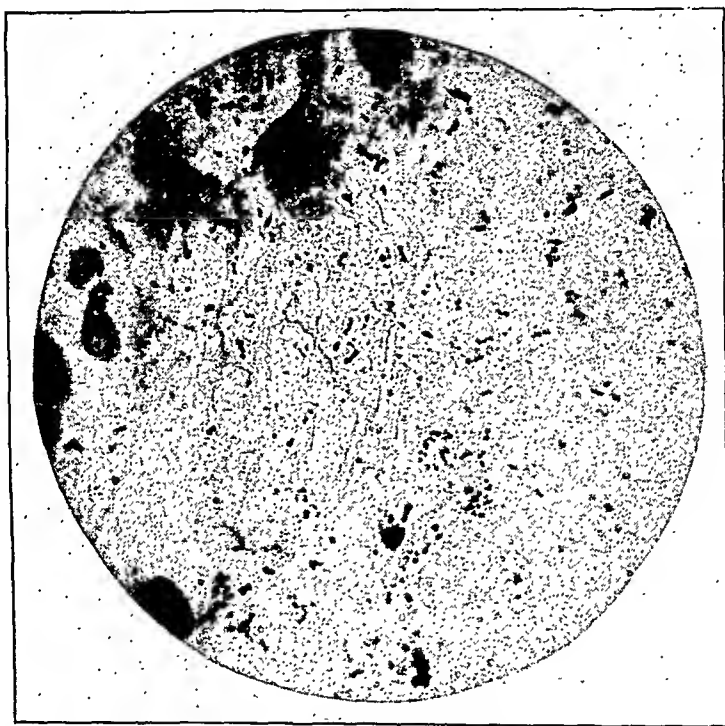


FIG. 2.—Smear from abscess of kidney medulla of rabbit produced by the injection of a streptococcus from an apical abscess.

The animals have been injected intravenously with 5 cc of the twenty-four-hour brain broth culture and killed in three to six days. Four hundred and sixteen rabbits have been injected and autopsied. Of this number 166 or 40 per cent showed gross lesions of the kidney (Table I). The pathological lesions encountered have been cortical abscesses, pyelonephritis, acute hemorrhagic nephritis, and subacute parenchymatous nephritis (Fig. 3, *A-F*, Fig. 4). By far the most common type of lesion has been pyelonephritis manifested as edema, necrosis, and abscess formation in the medulla of the kidney and usually extending well down to the tip of the papilla.

TABLE I.—LOCALIZATION OF BACTERIA ISOLATED FROM INFECTED TEETH.

Number of animals	416
Percentage of animals showing lesions in:	
Joint	57.0
Kidney	40.0
Muscle	29.0
Endocardium	17.0
Myocardium	12.0
Brain	9.0
Eye	25.0
Stomach and duodenum	10.0
Gall-bladder	0.2

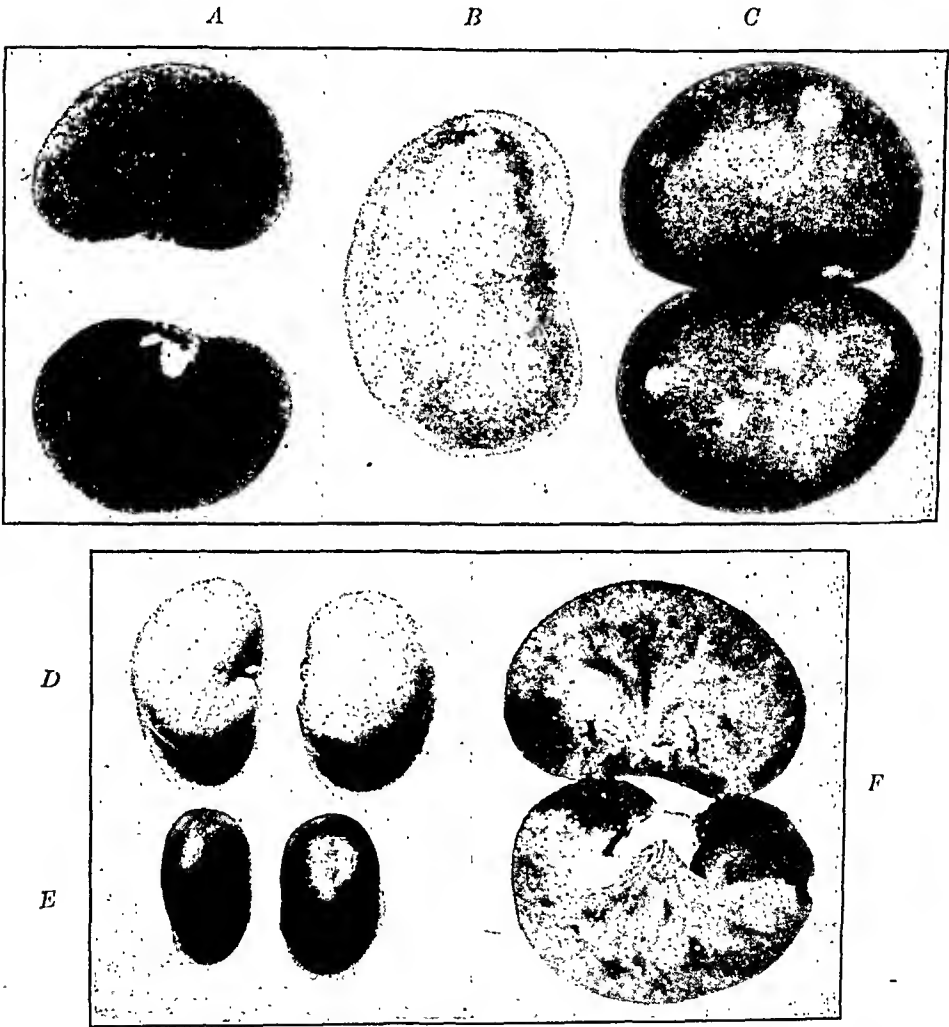


FIG. 3.—Types of lesions in rabbit's kidney produced by the intravenous injection of organisms from chronic dental foci. *A*, acute glomerular nephritis; *B*, acute glomerular nephritis and cortical abscesses; *C*, cortical abscesses; *D*, subacute parenchymatous nephritis; *E*, kidney of normal rabbit of same weight as *D*; *F*, typical lesions in kidney medulla. Note the areas of necrosis surrounded by hemorrhagic zone extending well into the tip of the papilla.

The frequency of kidney lesions occurring after intravenous injection shows clearly the great pathogenicity for kidney tissue of the bacteria recovered from chronic foci. The type of lesion produced most commonly in animals is that corresponding to the lesion occurring most frequently in patients, namely, a pyelonephritis.

Even with such evidence of the pathogenicity of the organisms from chronic foci the question remains as to what proof there is that the organism in question really causes in any particular patient the disease with which the patient presents himself. Certainly the most convincing proof we have of the relation of a focus to a disease is the reproduction in animals of the disease from which the patient

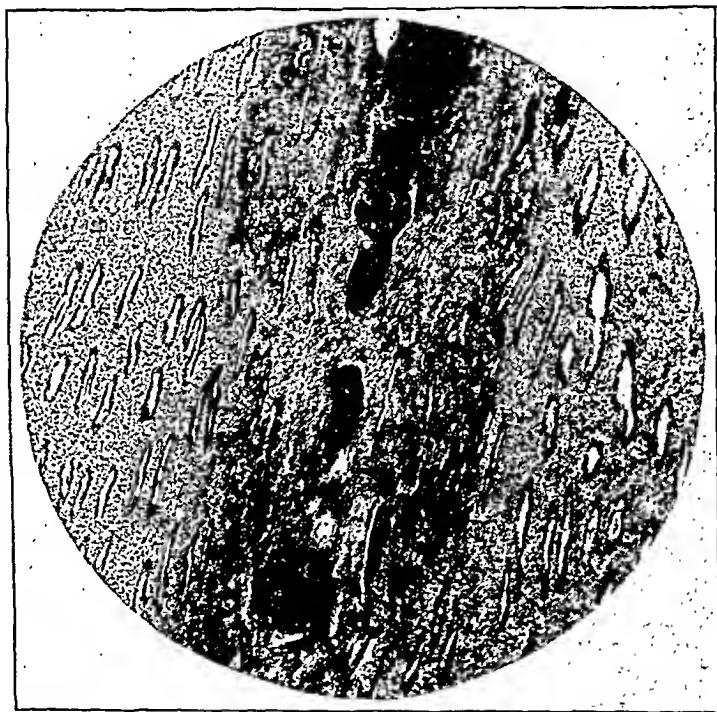


FIG. 4.—Photomicrograph through typical lesion in medulla shown in Fig. 3, *F*.

suffers with the organisms recovered from a chronic focus. Additional proof is afforded by the effect of the removal of the focus on the clinical course of the disease.

Six patients have been studied in this connection. The case histories and results of animal inoculation are given in detail below.

Case Reports. CASE I.—Mrs. J. A. P., housewife, aged forty-five years, Case No. 3702, had not felt well since a severe attack of influenza in 1918. At that time she had fever for twelve days without evident pulmonary complications. In May, 1922, she had an attack of pain in the left kidney region and a second attack in September, 1922. When first seen in October, 1922; the urine was

about one-third pus. There was a moderate amount of albumin but no casts. Stained smears of the urine sediment showed Gram negative bacilli.

The dental radiographs revealed five pulpless teeth but none showed definite rarefaction around the apex. All the pulpless teeth were extracted. Following the extraction the patient had a chill and an acute exacerbation of her symptoms. In January, 1923, lavage of the right kidney pelvis was done twice. Six rabbits were injected with the streptococci and staphylococci recovered by culture from the teeth; 2 rabbits showed no kidney lesions; 2 showed small hemorrhages in the cortex, and 2 developed multiple abscesses in the kidney medulla.

The patient has had no further symptoms and eight months after the teeth were extracted, the urine showed no pus cells or albumin.



FIG. 5.—Drawing of the kidney of rabbit injected with streptococci from apical abscesses in Case II.

CASE II.—M. I., housewife, aged forty-five years, Case No. 4524, had had frequent attacks of tonsillitis and quinsy before a tonsillectomy was done in May, 1922. She had had pyuria for twenty years and had been given pelvic lavage in 1915 without improvement. When first seen in January, 1923, she had been confined to bed for several months with myocarditis. Recently she had had an attack of acute arthritis, involving several of the larger joints. The physical examination was negative except for an evident myocarditis. The blood count showed 4,000,000 red cells, 10,500 white cells, and the following differential: Polymorphonuclear neutrophils, 59.6, eosinophils, 3.2, basophils, 0.6, lymphocytes, 32.2, and large mononuclears, 4.4 per cent. The urine contained a very large amount of pus, a moderate amount of albumin, but no red cells or casts.

The radiographs showed four pulpless teeth, only one of which had an area of apical rarefaction. The pulpless teeth were extracted. Green producing streptococci were recovered from all of them.

Four rabbits were injected with the cultures. All showed at autopsy multiple abscesses (Figs. 5 and 6) in the kidney medulla. All had purulent fluid in the joints, and five showed muscle lesions.

The patient was seen again nine months later. The heart and joint symptoms had disappeared. The urine contained only a small amount of pus. No local treatment had been given.

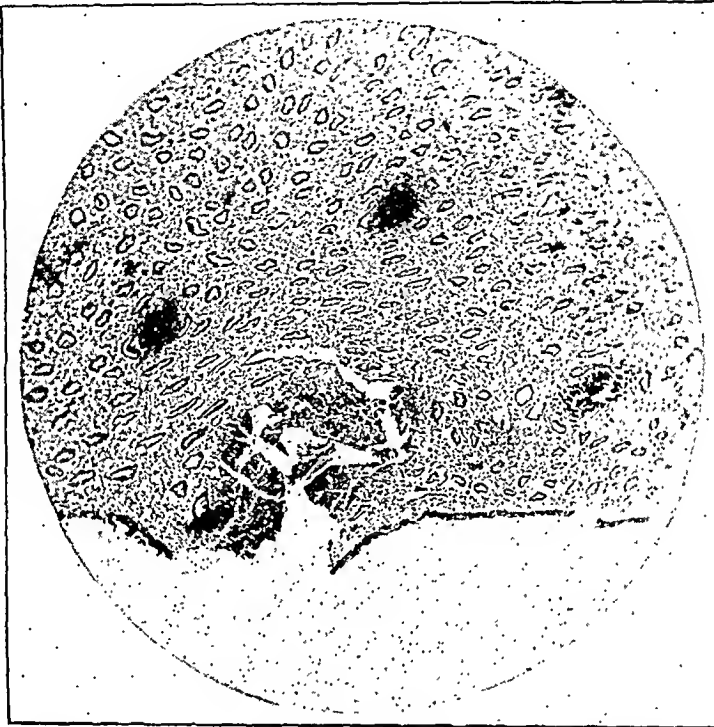


FIG. 6.—Low-power photomicrograph of portion of medulla of kidney shown in Fig. 5. Note the numerous small abscesses. One large abscess is breaking through the epithelium and discharging into the pelvis.



FIG. 7.—Roentgenograph of bicuspid tooth of Case III. The root canals are well filled, and there is no roentgenographic evidence of infection. A culture of the root tips showed a profuse growth of a short chain streptococcus.

CASE III.—C. B. P., dentist, aged thirty years, Case No. 437, had had bilateral pyelitis in 1917 which was relieved by local treatment. In January, 1922, the patient's tonsils were removed and a resection of the septum was done. In May, 1922, he had an attack of chills, fever and pyuria, followed by another in September, 1922.

The physical examination was negative except for undernutrition. The red cell count was 5,024,000 hemoglobin 100 per cent and white count 8200. The tonsils were cleanly removed.

The patient had only one pulpless tooth (Fig. 7). The roots were well filled and there was no rarefaction of bone at the root tips. A culture from the extracted tooth tip showed a large number of colonies of a green producing streptococcus (*S. salivarius*). Two rabbits were injected with this culture. One died in two hours and showed no lesions at autopsy. The other rabbit showed many small abscesses in the medulla extending down well into the papilla.

CASE IV.—W. W., a medical student, aged thirty-four years, Case No. 4274, stated that two weeks previously he had suffered from frequent burning urination, hematuria, chills and fever as high as 102° F. The symptoms improved at first under medication but the chills and fever recurred. He had had a similar attack nine years previously. There had been no other illness. The tonsils were cleanly removed. Physical examination was negative. The urine showed gross blood, many pus cells and a short chain streptococcus which was recovered by culture. One bicuspid tooth held a large inlay under which the pulp had died. There was no area of rarefaction at the tip. The tooth was extracted. From the tip a pure culture of a green producing streptococcus (*S. fecalis*) was obtained. Two rabbits were injected with the culture of the streptococcus. One showed at autopsy multiple abscesses in the pyramids and a purulent arthritis. The other showed an acute hemorrhagic nephritis and a few endocardial vegetations. The patient's urine returned to normal and there have been no further symptoms.

CASE V.—M. K., housewife, aged fifty-one years, Case No. 571, had suffered from arthritis, multiple onychia, attacks of palpitation and nycturia for many years. All these symptoms were relieved by the extraction of four abscessed teeth. Four years later the patient again presented herself because the onychia and heart palpitation had returned.

The physical examination showed marked swelling and redness around the nail root of one finger. The heart action was rapid. The sounds were distant with a tendency to gallop rhythm.

The dental radiographs showed areas of rarefaction around the roots of the lower right molar. The urine showed many pus cells and a trace of albumin. The blood count was normal. The Wassermann test was negative.

The infected tooth was extracted. The nail infection quickly subsided and the heart palpitation disappeared. A urine examination six weeks later showed no albumen or pus cells.

Cultures from the root tips showed a profuse growth of a non-

hemolytic streptococcus (*S. non-hemolyticus* 1). Eight rabbits were injected with this culture. All showed abscesses of the kidney cortex and in some there were abscesses in the medulla (Fig. 8).

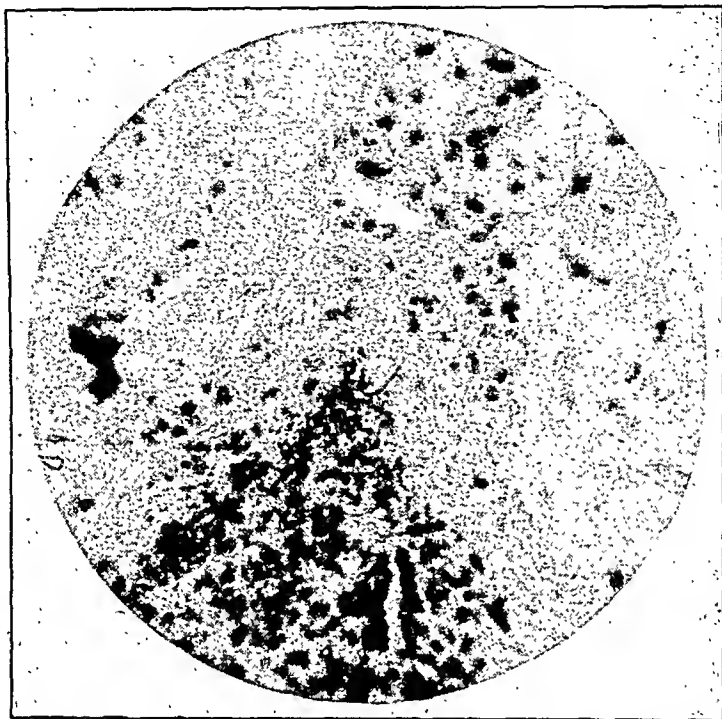


FIG. 8.—Streptococcus in medullary abscess of kidney of rabbit injected with the streptococcus from Case V (Gram stain).

CASE VI.—Mrs. L. P. E., a physician's wife, aged twenty-eight years, Case No. 7034, began to have pain in the second left lower bicuspid tooth about November 1, 1923. An inlay was removed, the root canal was treated a number of times, and a temporary filling put in. The first part of January the tooth was again painful for a week. She then suddenly began to have pain in the right kidney region. The temperature at this time was normal. The following day she had a chill, the temperature rose to 102° F., and the pain in the kidney region continued. There was some frequency of urination. The urine contained much pus and some Gram positive cocci. The fever continued for one week, the pyuria for three weeks.

Radiographs taken February 8, showed no destruction of bone or absorption from root tip of the lower second bicuspid. The peridental membrane at the tip was thickened. A root tip was present in the region of the left lower third molar. The bicuspid and the root tip were removed February 11. A profuse growth of a green producing streptococcus was obtained from both cultures.

Four rabbits were injected intravenously with 5 cc of the broth culture from the bicuspid and 2 with a like amount of the culture

from the third molar root tip. The 2 rabbits injected with the culture from the third molar showed no kidney lesions.

One of the rabbits injected with the culture from the bicuspid died soon after injection. The other 3 were killed after an interval of forty-eight hours. One showed many small hemorrhages and a few abscesses in the cortex and numerous abscesses in the medulla. The organisms were recovered by culture of the kidney. This animal also showed a few hemorrhages around the joint, and many abscesses in the myocardium. The other 2 rabbits both showed many abscesses in the medulla of the kidney with no lesions elsewhere.

Two rabbits were injected with streptococcus recovered from the kidney of one animal injected with the original culture. One showed at autopsy many abscesses in the kidney medulla with no lesions elsewhere. The other showed similar changes in the kidney and abscesses in the muscles, iritis and hemorrhages in the duodenum.

Discussion. The high incidence of kidney lesions in rabbits following the intravenous injection of bacteria recovered from chronic foci of infection demonstrates clearly that such organisms are very pathogenic for the kidney. It is an accepted fact that bacteria are often being fed into the blood stream from such chronic foci as alveolar abscesses. These facts show the importance of chronic foci in relation to kidney disease of bacterial origin.

The fact cannot be too strongly emphasized that in a patient with kidney disease of focal origin, the dental radiographs should not be relied upon to eliminate the possibility that the infection has arisen from infected teeth. This is well illustrated in Cases III, IV and VI in this series. Cultures from several hundred pulpless teeth which showed no radiographic evidence of infection, demonstrate that approximately 40 per cent harbor bacteria in sufficient number to be a possible focus of systemic disease.

Twenty-eight rabbits have been injected with the cultures from the 6 cases here reported; 24, or 89 per cent, developed gross kidney lesions. Only 40 per cent of the animals injected with bacteria from the whole group of patients (Table I) showed kidney lesions. This very much higher percentage of kidney lesions with cultures from patients who had kidney disease, shows clearly that the organisms in the infected foci here had acquired some special affinity for kidney tissue. This with the fact that the animals usually developed lesions similar to these from which the patients suffered, seems most suggestive of a causal relation of the dental infection to the kidney disease. The improvement in the patients' condition following the removal of the chronic foci makes the connection most probable.

Summary. In summary I should like to emphasize the following points:

Pyogenic kidney infection is almost always of hematogenous origin.

The pathological picture is variable and cannot be determined from the clinical symptoms.

The so-called pyelitis in the absence of obstruction is almost always a pyelonephritis.

The colon bacillus is probably seldom the primary invader except possibly in cases of lower urinary tract obstruction.

The infecting agent is usually a streptococcus or staphylococcus which produces lesions by reason, either of great virulence or an especial affinity for kidney tissue acquired in a chronic focus.

In a great majority of cases of chronic pyogenic kidney infection the organism is fed into the blood stream from chronic foci of infection.

Six cases are reported in which kidney lesions similar to those from which the patient suffered were produced in animals by the intravenous injection of organisms recovered from infected teeth.

The need for the proper consideration of chronic focal infection in treating such cases of kidney infection is apparent.

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THE MOTHER'S MILK AS A SOURCE OF INFECTION IN EPIDEMIC PEMPHIGUS NEONATORUM (IMPETIGO CONTAGIOSA BULLOSA).

BY RALPH R. MELLON, M.D., DR. P.H., DOROTHY CALDWELL, M.Sc.

AND

W. W. WINANS, M.D.,

ROCHESTER, N. Y.

(From the Department of Laboratories and the Department of Obstetrics,
Highland Hospital.)

It is our intention in this paper to show that the breast milk of certain mothers may contain large numbers of *Staphylococcus aureus*, thus constituting a possible, albeit unrecognized source of infection for the newborn. Of the six outbreaks occurring in this hospital in three years, four seemed to originate from such milk,

a fifth was traced to an infected burn of the skin, while the origin of the sixth one was uncertain. The observations were the result of an attempt to clear up some of the interesting uncertainties regarding the mode of spread of the infection and the reasons for its persistence in institutions, once a foothold is obtained.

It is not desired to make an extensive review of the literature, which has been thoroughly covered in the review given by Foerster,¹ and also to some extent in the paper of Cole and Ruh.² A preliminary report by the writers has already appeared.³

One of the outstanding features of epidemics of this kind in institutions is their tendency to reerudescere after protracted periods of quiescence. The presumption has been that the infecting organism, namely, the *Staphylococcus aureus*, is particularly viable or that the hygienic conditions in the institution have been lax, or that perhaps both factors have played a part in the recurrences. On clinical grounds it has been regarded as fairly certain that the infection can be transferred from children to adults, and *vice versa* by direct contact. Certainly the view is quite reasonable, especially in light of the well-known proclivity of the organism in question for the skin.

The evidence, however, for transfer in other ways than by the direct method, together with evidence for the systemic character of the disease at times, may have a distinct bearing on the well-known persistence of the condition as well perhaps as for some of the recrudescences. We know, for example, that Della Favera⁴ and Hofmann⁵ have isolated the coccus from the blood stream, and the organisms are not uncommonly found in the blood of cases of Ritter's disease, which is regarded by some as simply a more malignant type of pemphigus. It appears, too, that in some cases of sepsis in the mother a pemphigoid condition of the skin may develop, as is evidenced by the studies of Staub,⁶ Fehling⁷ and Prissman.⁸ Foerster, who quotes the work of these writers, rather regards such cases as examples of bullous exanthemata occurring in the course of septic conditions and so excludes them from the condition under discussion. Our observations suggest, however, that such segregation is of rather doubtful propriety.

As far then as the epidemiology of the question is concerned, it may be stated that, although it is not difficult to account for transmission during an epidemic, once it is started, it is often particularly difficult to find the source of the infection as well as to account always for the recrudescences.

For this reason we have been especially concerned in studying carefully the *initial* cases of each outbreak which has followed a period of quiescence. Our attention in such cases has been focused on the mother also, on account of the evidence from our first case suggesting that through her milk she was a carrier of the infection.

BACTERIOLOGY OF MOTHER'S MILK IN A SPORADIC CASE OF PEMPHIGUS NEONATORUM. The lesions of the baby were first noticed

on the thighs, appearing on the eighth day after birth. Three days later the face and head were involved. The lesions began as typical blisters, most of which later developed to the pustular stage. Following rupture of the vesicles a marked desquamation took place over areas several centimeters in diameter, leaving a moist reddened substratum. The lesions on the face and head developed about the same time that the baby was taken off the mother's milk. They disappeared within a few days.

As soon as the lesions were discovered on the baby attention was directed to the mother. It was learned that about the fifth day following delivery she developed a mildly erythematous type of itching rash, which appeared first on the arms about the elbows and was quickly followed by the same type of lesion on the legs and on some other portions of the body. At no time did any rash develop on the face. With the exception of the skin of one breast, where a few of the most minute whiteheads or pustules later developed, nothing resembling impetigo was present on the mother's skin. The rash itself occurring in an obstetric patient was not such as to excite any special attention, and resembled nothing so much as an ordinary drug rash. Over the shoulders it took on a macular appearance and on the arms and legs was more of a diffuse erythema. In three or four days it was gone.

For reasons which will appear later on, in connection with the first case that occurred in this institution a culture of the milk was made first under aseptic conditions. The nipple and areola were first thoroughly washed with green soap and then with bichloride, which was followed with boric acid. With a sterile breast pump 5 cc of milk was withdrawn and immediately cultured on a blood-agar plate with a 3-mm. platinum loop. Approximately one hundred colonies of pure *Staphylococcus aureus* and *albus* developed. The colonies were surrounded with a broad zone of hemolysis and those of the *aureus* greatly outnumbered the *albus*. At this time one or two of the most minute pimples were observed on the breast, and culture of these yielded the same organism. No cracks in the nipple were apparent.

The question then arose regarding the origin of the organisms within the breast. Did they come from the blood or were they introduced from the skin? Perhaps this question can never be answered with finality, yet the evidence rather points to the former alternative. We also wished to know whether the organisms were growing in the ducts of the nipples alone, or if they were generally disseminated throughout the glands. To obtain some idea of this we first obtained about 5 cc of milk from both breasts—fractions *A* and *B*; these were put into sterile containers and then practically all of the remainder of the milk withdrawn from the breasts and discarded. With fresh sterile pumps the residual fractions—*C* and *D*—were withdrawn. Assuming that we had by now thoroughly washed out the peripheral ducts, the residual frac-

tions were held to be derived from the deeper recesses of the breasts. The four fractions were streaked on separate quadrants of the same blood-agar plate, and they showed approximately equal numbers of the organism in almost pure culture. In spite of the abundance of organisms present, and their apparent wide dissemination throughout both breasts, no evidence of mastitis was found either clinically or from microscopical examination of the centrifuged sediment. Cultures of the blood, throat, stool and cervix were negative for the specific organism. In fact, a culture of the cervix grew no organism, so it was highly improbable that the vaginal tract was the portal of entry. The catheterized specimen of the urine, however, showed a few colonies of the organism. These findings, together with the rash which occurred rather generally over the body within a short space of time, suggest that the infection, mild though it was, was systemic in character.

Specific inquiry regarding the possible source of infection failed to reveal any very positive evidence. The patient did say that a sweater borrowed from a family in which there were several children was worn by her for a few days following delivery, after which she noticed an irritation on her arms to such an extent that the sweater was removed. Simultaneously the rash appeared on her neck. It could not be established that the children in the house from which the sweater was obtained had infection of any sort, and its connection with the development of the rash may have been pure coincidence. However, it is very much to the point that at the time of entrance of the woman to the hospital numerous cases of this disease were present in the community, so it would seem probable that she brought the infection with her, perhaps as a carrier. Careful segregation of both mother and infant prevented further cases of the condition in the hospital. To our knowledge at least one case of Ritter's disease existed in the community at this time.

We then directed our attention to the probable route of infection in the baby. Inasmuch as the milk was so heavily infected, it was logical to believe that the organisms might have passed through the intestinal canal, and their elimination in the feces have been responsible for the initial lesions that occurred on the thighs of the infant. This theory of the mechanism of infection was made decidedly improbable when a culture of the stools of the infant was found negative as far as the *Staphylococcus aureus hemolyticus* was concerned. Furthermore, had the infection been presumed to have arisen by direct contact, one would have expected it to occur first about the face of the infant, because while nursing it made daily contacts with the skin of the mother's breast, the minute pustules of which were proven to contain the infective organism. The fact that the infection of the face and head did not occur until several days after the appearance of the lesions on the thighs was rather against the theory of direct contact. As soon as the baby

was taken away from the mother's milk it immediately began to improve, and the lesions of the face cleared up completely in less than forty-eight hours, and as was to be expected the baby made an uneventful recovery.

If we are to assume that the organisms ingested by the infant in the milk produced a systemic infection, it would seem that they must have invaded the intact mucosa of either the upper respiratory or the gastrointestinal tracts. In confirmation of this point, we were already in possession of the following experimental evidence which we had obtained about a year previously. Freshly isolated cultures of some the more severe cases of the epidemic of this condition, which began in January, 1922, were fed to young guinea-pigs in milk (Table I).

TABLE I.—PROTOCOL OF FEEDING EXPERIMENTS.

Feeding-date, 1922.	Guinea-pig No.	Age of pig.	Feeding duration.	Result.	Culture.
Feb. 9	385	3 days	4 days	Died, Feb. 12, 1922; massive pneumonia in both lungs	Heart blood negative Staphylococcus aureus in purity from lung.
Feb. 9	386	3 days	4 days	Died, Feb. 13, 1922; massive pneumonia in both lungs	Staphylococcus aureus from both lungs in purity.
Feb. 10	387	4 days	15 days*	Died Mar. 2, 1922; abscess; sepsis; no pneumonia	Staphylococcus aureus in heart's blood.
Feb. 14	388	Full grown	10 days	Negative; died, Feb. 24, 1922, of guinea-pig pneumonia	Mixed infection apparent from smears of bronchi; no growth on Difco agar.
Feb. 14	389	Full grown	10 days	Negative; died Apr. 28, 1922, of typical guinea-pig bronchopneumonia	No cultures.
Feb. 17	392	17 days	7 days	Negative; died Apr. 28, 1922 of guinea-pig pneumonia	No cultures.
Feb. 20	393†	Full grown‡	Not fed	Died, Feb. 20, 1922, 11 days after first feeding of off-spring	Pure culture staphylococcus from lung.
Dec. 23	493	9 days	13 days	Negative; strain is now about a year old	
Dec. 23	494	9 days	13 days	Negative; strain is now about a year old	

* Then inoculated 5 cc subcutaneously.

† Presumably contracted the infection from a nursing pig, inasmuch as it gave suck to Nos. 385, 386 and 387. Nos. 385, 386 and 387 received cultures freshly isolated from cases of pemphigus neonatorum. No. 388 received a culture derived from the lungs of No. 385. Nos. 389 and 392 received cultures from the lungs of No. 386. Nos. 493 and 494 received fresh cultures of the same strain as No. 385.

‡ Mother of Nos. 385, 386 and 387.

TABLE II.—FRESHLY ISOLATED CULTURES FROM MILK OF WOMAN DESCRIBED IN TEXT.

Feeding-date, 1923.	Guinea-pig No.	Age of pig.	Feeding duration.	Result.
May 2	523	9 days	15 days	Negative.
May 2	524	11 days	14 days	Negative.
May 2	525	3 days	2 days	Pig died, but so mutilated by his fellow pigs that no autopsy was possible.
May 2	526	1 day	12 days	Negative.
May 2	527	1 day	12 days	Negative.

Animals Nos. 385 to 393 inclusive and Nos. 493 and 494 were fed morning and evening with 1 cc of 0.9 NaCl suspension of the organisms, about 5,000,000,000 to 1 cc. A medicine dropper was used. Pigs Nos. 523 to 527 were fed in the same way, but milk was used as a menstruum instead of NaCl.

Of the 3 pigs first treated, ranging in age from three to four days, 2 died in less than a week, and much to our surprise the lesions found at autopsy were those of diffuse double pneumonia. From these lungs the staphylococci, which could be seen in large numbers, were readily isolated. One of the adult pigs that suckled the young ones while the latter were being fed the infected milk in some unknown way contracted the pneumonia, and from the lungs of this pig also were recovered the staphylococcus in purity. Three grown pigs fed for ten days showed no immediate effects, but in two months died of typical guinea-pig pneumonia. The young pigs died after four days' feeding. It should be stated that when pigs Nos. 385, 386 and 387 died we were not having other pigs die of spontaneous pneumonia. Pigs Nos. 388, 389 and 392 succumbed to this disease at a somewhat later period.

It would seem, therefore, that these organisms passed through the intact mucosa of these animals and were filtered out by the lungs, where in some cases their presence set up an active inflammatory condition resulting fatally. Whether the organisms were absorbed from the upper part of the respiratory tract and passed down the tracheal lymphatics, as is now regarded by some as a pathway for the development of pneumonia, or whether they were absorbed from some part of the gastrointestinal tract, cannot be stated.

The whole question of the passage of organisms through the intact mucosa of the gastrointestinal and respiratory tracts is one of great interest and considerable work has been done on the subject. Usually, however, avirulent organisms easily recognized culturally have been employed, as was the case with the work of Williamson and Brown,⁹ in the Mayo Clinic, with *Bacillus prodigiosus*. Many of these experimental results have been negative,

and it would seem that the virulence of the organism would be of first importance in such work, especially if we regard virulence as the capacity of the organism to multiply in the tissues. In support of our opinion in respect to the relation of the virulence of organisms to their passage through the intact mucosa, we quote the work of Thiele and Embleton,¹⁰ who were unable to demonstrate the presence of *Bacillus mycoides*, *Bacillus coli* and *Bacillus prodigiosus* in the blood stream after feeding, while anthrax bacilli were found in the lungs and urine four hours after feeding.

In the same connection it was of considerable interest that the cultures which gave us positive animal results soon after isolation were completely negative when tried on young guinea-pigs about a year later, after the cultures had been kept on artificial media (Table I, pigs Nos. 493 and 494). It was of interest, too, that we failed to repeat the results with fresh cultures of the organism from the case just described (Table II). Therefore we are inclined to draw the conclusion that the organism was of slight virulence, as indeed was to be suspected from the mild character of the reaction both in the mother and in the child: The cases were by no means as alarming clinically as the earlier ones.

RESULTS OF SUBSEQUENT OUTBREAKS. No further cases of the disease occurred until August, 1922, when another single case occurred with findings very similar to the one studied, except there were not nearly so many organisms in the mother's milk. However, they were pure *Staphylococcus aureus*, while the milk of other mothers cultured at this time were either negative or showed an occasional colony of *Staphylococcus albus*.

An outbreak of 10 cases occurring in October, 1923, gave opportunity to study the milk of numerous mothers, both those having infected babies and those with normal babies. This was especially desirable if we were to verify our suspicion that single cases, such as have been described, might form starting-points for other cases. It was of interest, then, that here again we found that the mother's milk of the first baby to come down contained pure *Staphylococcus aureus* in considerable numbers. This was also true of the mother's milk in one other case in this outbreak. All other mothers or cases were either negative or had a few colonies of *albus*. In addition the milk of six mothers with normal babies showed the same negative findings. The cocci were identified culturally, chiefly by pigment production and reaction to mannite, and serologically by the agglutination reaction. One other small outbreak showed similar findings.

Perhaps the most striking instance of all was the latest outbreak, July, 1924, which involved not only the mother's own baby (Baby Z), but also a seven months' premature infant (Baby V) fed with the same milk, because the premature's mother had practically no milk. Baby V, the premature, was born two days after Baby Z,

and on the same day both babies developed the skin lesions of pemphigus, Baby V having a few scattered pustules and Baby Z having one large vesicle on the back of the neck. From the lesions of both babies *Staphylococcus aureus* with a few *albus* were found in abundance. It is of note that clinically the premature did not tolerate the milk of the Z mother, as was evidenced by a rapid rise of temperature with gastrointestinal symptoms. These results in Baby V recall the feeding experiments with young guinea-pigs. After thirty-six hours it was given artificial feeding. No further lesions developed.

Except for the above sequence of events there would have been no reason to have suspected the mother, who was in splendid health and possessed an abundance of milk. Nevertheless, her milk obtained under rigid aseptic precautions yielded about twenty-five colonies of *Staphylococcus aureus* and a few *Staphylococcus albus* from our 2-mm. platinum loop seeding of an uncentrifuged sample. She had no lesion of any sort about the nipple or skin of the breast.

For control purposes it is of interest in this connection that a woman who had a small *Staphylococcus aureus* abscess in the subcutaneous tissue near the nipple yielded a milk with no *Staphylococcus aureus*. Her baby, too, was normal. This small outbreak above referred to occurred following a quiescent period of more than two months. The isolation precautions taken with both mother and children have prevented any new cases, which has been repeatedly shown in our experience to justify the procedure. It appears that early recognition of even mild cases and their rigid segregation, together with the mother whose milk contains the organisms, is of primary importance in preventing spread of a disease *that at intervals is being introduced anew into the institution*.

The results that may follow in the wake of unrecognized infection of *Staphylococcus aureus*, regardless of their source, is illustrated by the following outbreak originating apparently from a burn. It resulted in 6 cases, which in a week or so were followed by at least 12 more.

OUTBREAK TRACEABLE TO A SKIN INFECTION FROM A BURN. This small series of 6 cases occurred in February, 1924, the initial case being a baby on whose chest a mild burn developed, caused by a mustard plaster. The infection was pure *aureus*, and then quickly followed 5 other cases, apparently contact infections. The mother's milk in the initial case was negative, however, as was to be expected, indicating that the origin of two such outbreaks might be quite different.

SEARCH FOR THE EPIDEMIOLOGICAL TYPE OF STAPHYLOCOCCUS AUREUS. The outbreak following the burn case indicates that *Staphylococcus aureus* from pathological processes other than pemphigus may give rise to the disease, in which event we would

not expect to find by serological methods an epidemiological type of infecting aureus. This latter consideration was entirely borne out by study of many strains of *Staphylococcus aureus* of diverse origin which we have collected in the past three years. The detailed study will be reported separately. In this connection it is pertinent that covering a period roughly coinciding with that of the pemphigus outbreaks we have frequently isolated *Staphylococcus aureus* from lesions in almost every part of the body. This fact testifies for the systemic transfer of these cocci but without active sepsis, and makes it entirely conceivable that in the breast milk of the mother suffering from the rash, the origin of the cocci may have been hematogenous.

Discussion. Infection by way of the milk was suggested to us by the first case of the disease that was brought into the institution in the first week in January, 1922. The significance of the findings was not apprehended at the time, partly because the condition was not even known to be epidemic in the locality and partly because the mother was mildly septic. In this instance the mother developed a rather severe sore throat on the day of delivery, from which a staphylococcus was isolated from among the other organisms present. She also developed a septic type of temperature which ran for several weeks and a staphylococcus was isolated from her blood stream early in the course of the infection. About the fifth day a slight itching rash appeared, distributed irregularly over the body, but no lesions were discovered on the breasts. The rash was not as marked as in the 1923 case, and there was no evidence of pustule or vesicle formation. Like the other rash, it was rather evanescent in character.

Following the appearance of the coccus in the blood on the third day after delivery the lesions of typical pemphigus appeared on the baby on the ninth day, or four days after the rash first showed on the mother. This case did not come to our attention until other cases began to appear, and it could not be ascertained with certainty whether the latter originated from the mother or child of the first case, or whether they were of independent origin. The cultures of the child were of the same *Staphylococcus aureus* hemolyticus, as indeed were all the subsequent cases cultured, which numbered approximately two dozen. Before we became aware of the significance of the situation the mother with the blood infection left the hospital, and it was not possible to study her further. Although no cultures were made of the milk, it was surmised that infection in the baby might have occurred through it, since the coccus was present in the blood and since there were no other lesions apparent whereby the child could have gotten its infection from the mother. It seems reasonable to assume that for the past two years hemolytic staphylococcus infections have been epidemic, which is entirely comparable with the cadences of virulence so characteristic of the diphtheria bacillus and other epidemic organisms.

We emphatically do not desire to convey the impression that the majority or even a great number of cases of pemphigus neonatorum have had their infection transmitted from their mother's milk. Since this method of transmission has not been a recognized one, it is enough for preventive purposes to show that it may *sometimes* occur; for it must be obvious that any number of babies might have been infected from this one mother, even while her own child was still rigidly isolated. In such event responsibility might have been directed toward those having direct charge of the infant's segregation, resulting in the same confusion that always occurs when the real source of infection and its transmission are hidden.

Summary. 1. The evidence submitted is at least presumptive that certain outbreaks of pemphigus neonatorum are traceable to an initial case infected by its own mother's milk.

2. Such findings occurred three times in sporadic cases that might have given rise to outbreaks had not the mothers been segregated, while in a third sporadic case with these findings an outbreak of ten cases actually did result.

3. A similar outbreak was also traceable to a burn infected with aureus, suggesting a diverse origin for the infecting cocci.

4. No epidemiological type could be associated with the disease, the organism being serologically the same as those isolated from abscesses, etc.

5. When the *Staphylococcus aureus* is rampant, as it has been for several years, it may be present in the milk and even in the blood stream of certain mothers with few or no symptoms, who may be viewed as "carriers."

6. The mild infection in one mother resembled in no way true impetigo, which fact fails to support the theory that pemphigus neonatorum and impetigo contagiosa bullosa are identical diseases.

7. By concentration of attention on this means of transfer we do not intend to minimize the predominant role played by case to case contact, undoubtedly the common method of transmission in institutions, but from a public health standpoint it would seem highly important to isolate both mother and child when it can be shown that the mother harbors the infecting organism.

SUPPLEMENTARY NOTE. Since this paper was submitted for publication some time ago it is of interest that we have had another single case of the disease. It occurred about December 1, and has been the only case since last June in an obstetric service that has about seventy-five deliveries a month. Furthermore, the nurseries are overcrowded.

The infant referred to had numerous pustules, but no constitutional symptoms. *Staphylococcus aureus* and *albus* were obtained in moderate numbers from both breasts of the mother. In this case the infant recovered without artificial feeding. The infection is undoubtedly mild enough in some cases that it is conceivable

that some infants might escape entirely if the number of cocci ingested was not too large. However, our control series have not happened to reveal such cases.

It is of note that careful segregation of both mother and infant, has resulted in no further cases, after thirty days, despite the fact that several cases of *Staphylococcus aureus* sepsis and other aureus infections from the surgical departments have been in the hospital.

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SYSTEMIC REACTIONS TO ORAL INFECTION.*

BY JOHN WILLIAM DRAPER, M.D.,

AND

REDFORD KOHLSAAT JOHNSON, M.D.,

NEW YORK.

Biological Considerations. Even the most casual study of the relationship between general pathological processes and oral infection presupposes at the very least a certain knowledge of the origin and development of the teeth. Hertwig¹ says: "From a morphological point of view the teeth can well be designated as the most interesting structures of the oral cavity. Their development in man and mammal is accomplished in a manner which is neither simple nor easily intelligible; in the lower vertebrates, on the contrary, it is simpler." Mammalian teeth are limited in attachment to the entrance of the alimentary tube, whereas in the lower vertebrates teeth are characterized by a very wide distribution. Here they often cover not only the roof and floor of the oral

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cavity but occur also in immense numbers as palatal, lingual and pharyngeal teeth. They extend also in close-set rows over the whole surface of the skin, producing, as in the Selachians, a strong coat of mail. These primitive teeth are simply ossified papillae of the skin and the mucous membrane, upon the contiguous surfaces of which they are formed. Shull,² speaking of the origin of teeth, says: "In some species (of the roundworm), tooth-like structures may be developed in the mouth cavity," and in the frog he states that the upper jaw bears teeth which serve to hold the prey when caught.

It is rather generally conceded that the organs which we commonly refer to as teeth, implying thereby masticatory function, phylogenetically are found first in the Selachians. Here the teeth occupy the edges of the jaw, serve for the comminution of the food and take their origin, not on the surface of the mucous membrane, but in its depths. However, in the Selachians the replacement of teeth by new ones throughout life is retained and remains as an unlimited process. Intense specialization of any organ bears a well-known relation to its function and to its stability. As the number of teeth in mammals have become reduced and as they have become more and more highly specialized, obedient to inexorable law, all that they have gained in function has been lost in power of replacement and of resistance to infection. Consider the highly specialized dinosaur, extraordinary in size, strength and structure, and the lowly modern crocodile, his sole remaining and decadent relative. The one took possession of the earth for a brief time, only to perish; the other lives on in slime because incapable of change.

Another biological consideration bearing upon the relation of the teeth to generalized human pathology is that of symmetry. The bilateral symmetry which characterizes all the higher forms, mammals in particular, has been undoubtedly evolved for the purpose of rapid motion. Man, cut by an antero-posterior plane, presents two mirrored halves. His sole asymmetrical system is the alimentary canal. Nor is this wholly without bilateral symmetry. No part of the body is more symmetrical than the teeth, both as regards distribution and bilateral identity of structure. The far-reaching importance of symmetry in animal form has been demonstrated by Hambidge,³ who recently rediscovered the law of dynamic symmetry and its relation to the "whirling square." He proved that so seemingly divergent entities as the human skeleton and a Greek vase conform equally to this law. T. K. Hanna,⁴ the well-known illustrator, states that the Egyptians were familiar with it and passed it on to the Greeks. The conformation of Greek art and architecture to the dynamic symmetry of living things is the fundamental explanation of their inimitable beauty. Deviations from this law, as in the case of asymmetrical dentition and asymmetrical antral development, are closely associated with liability to

infection. The recognition of such laws and of their applicability to the problems of modern medicine shows the trend of future research.

Originating in epithelium, which is the point of origin of all protective, secretory, excretory and absorptive organs, the teeth, as conceded above, and in common with certain other epithelial structures, are peculiarly liable to microbial invasion. This may be due also, in part, to their superficial position which often results in minute erosions. It is worth much more than a passing thought to note that most of the important areas of focal infection are of epithelial origin. It must be borne constantly in mind that the various systems of the body are intimately related and that no unit can be properly discussed as to form or function, without considering probable correlated involvement of one or more of the remaining units. Particularly in the consideration of oral infection there should be stressed the study of the *body as a whole*.

Reviewing these biological considerations, there are few if any structures in the body more ancient or more highly specialized than the teeth. For this they pay a price. Had they remained the simple, superficial, replaceable organ of the lower vertebrates, or higher invertebrates, there doubtless would be today no problem of oral infection. For the penalty of specialization is inexorable. The chambered nautilus has remained unchanged since silurian days, being rewarded for its lack of initiative by relative immortality. The commonplace is preserved, while exaggerations, good or bad, are swept away. As Shull, in discussing these problems says: "The paths of glory lead but to the grave."

Frequency of Associated Infections. It is rare indeed to find a patient suffering from focal infection in whom the areas of infection are not multiple. This doubtless was known to Billings, to whose clinical studies we owe much of our present knowledge of the fundamental cause of most disease syndromes; and also to Adami, whose pathological reseaches led him, twenty years since, to the promulgation of the well-known theory of "subinfection." The term oral infection properly implies not only dental and tonsillar lesions but also paradental infections. For the more one studies this problem of the sequence and the correlation of oral lesions the more convincing is the evidence that chronic maxillary sinusitis is not only very frequent in occurrence but is also often directly of dental and remotely of tonsillar origin. It is important therefore to look upon all the sinuses, clinically, as closely associated with the oral cavity. There is much evidence that sclerotic changes or a condensing osteitis developing in the structure of the maxilla will, in a large percentage of cases, spread to the contiguous floor of the antrum. Unless the degenerating tooth is removed, the end-result is likely to be chronic maxillary sinusitis. (See Fig. 1.)

Elective Localization and Susceptibility. As clinicians we have found this part of the problem extremely perplexing. To Vaughan⁵ we owe much of our knowledge concerning specific ferments of the cellular components of the body. Roger,⁶ of Paris, has also dis-



FIG. 1.—Chronic scleropurulent maxillary sinusitis (left), resulting from severe upper left periodontal infection.

cussed this matter comprehensively, and in this country Rosenow has emphasized the law of specificity. Recently Price,⁷ in a monumental monograph which bids fair to revolutionize our entire understanding of the importance of dental lesions, brings the matter up to the present day. Manwaring and Boyd,⁸ studying bacterial toxins by means of the isolated mammalian heart, conclude that streptococcus filtrates are markedly toxic toward both the conducting and contractile tissues. Cotton⁹ has demonstrated the relation of dental infection to insanity.

Summarizing these essays in terms of our own studies, it is clear that the organisms responsible for dental infection, particularly those of the so-called "rheumatic group," show a consistent and unvarying specificity in their behavior, not only toward the tissues of experimental animals, but toward those of man as well. It is well known that hereditary susceptibility is a factor of the utmost importance, when considering the specific relationship between "rheumatic group" organisms and lesions of the cardiovascular and joint tissues. That heredity and specificity are also of importance in considering lesions of the brain with its resultant functional disorders has been shown by Cotton. The mechanism for the production of toxic cerebral lesions is the same as for the production of "rheumatic" heart and joint lesions. In both cases the specific localization of the organism is aided by the inherited susceptibility of tissue.

Hemic Cellular Components. Considering the normal percentage of large and small lymphocytes to run from 21 to 38 per cent and the polymorphonuclear neutrophils from 60 to 70 per cent,¹⁰ in the average adult individual, it is evident that there are certain well-defined and definite changes in the relative proportion of these cells nearly always to be found in adult patients harboring focal infection. The occasional exception to this rule is probably due to the fact that the hemopoietic functions of the body have not yet been put out of equilibrium by the toxicosis. Bearing in mind the warning given by Bass and Johns,¹⁰ that whenever the total number of a given kind of leukocyte is increased or decreased the percentage is affected accordingly and that what may be a low percentage for a given cell may in fact not indicate an actual loss of such cells, but on the contrary an increase in other cells or *vice versa*, we have analyzed our laboratory reports from 35 patients presenting definite evidence of colon-streptococcus focal infection with the following results: Average number of total leukocytes 6183; average percentage of polymorphonuclear neutrophils 49 per cent and of lymphocytes, large and small, 45.6 per cent. A similar analysis of a group of 44 adults not presenting evidence of focal infections shows the average blood count to be as follows: Total leukocytes 8440; polymorphonuclear neutrophils, 66 per cent and total lymphocytes, 33 per cent.

RELATIONSHIP OF ORAL INFECTION TO SYSTEMIC DISORDER

Case No., sex, age.	Chief complaint.	Oral findings.	Other findings.	Treatment.	Result.	Remarks.
1 4281 M. 26	In 1916 constipation; headache; increasing drowsiness, incoordination, incapacity; personality deterioration; marked irritability. In 1922 bowels much better and generally improved, but not well	Not studied at this time; infected teeth, 8; chronic scleroperiosteal sinusitis	Six-day delay in roentgen-ray emptying of colon; 9-hr. gastro emptying and terminal ileal delay; chronic pericolitis; segmental colitis; roentgen-ray of gall tract, moderate colon delay; tonsils infected	Subtotal colectomy; both right and left sides; 8 teeth removed; both antra opened and everted; tonsillectomy	About 50 per cent improved; able to hold his job but no more; stationary for 6 yrs.; reexamination in 1922, immediate improvement; cessation of all residual symptoms; is now running own business	Drug clerk; butt of ridicule for other clerks because of stupidity and quantity of castor oil taken; constantly demoted and about to be discharged as useless; colon should have been operated on last, not first; illustrates progress made in studying such cases as a whole.
2 5701 M. 77	Sudden alarming loss of vitality; had not been sick since early youth; generalized pain, sleeplessness and anorexia	Severe apical infection and peridental infection of 6 teeth; sinuses not studied	None at that time	All dental infection removed	Complete restoration to normal in 2 mos.	Farmer; life-long activity both mentally and physically; able to return to outdoor work and public speaking; sick again 5 yrs. later; tonsils removed; normal and improved at 80 yrs. of age.
3 4460 M. 50	Dyspnea on exertion; precordial pain; irregular heart; weakness; nervousness; insomnia	Very severe pandental infection; sinuses not studied	Cardiac arrhythmia; true angina	Removal of all teeth and necrosed bone under general anesthesia	A temporary improvement in subjective symptoms	Sudden death 1 yr. later; sclerosis of coronary arteries and degeneration of the heart muscle.
4 5745 F. 47	Paranoid ideas; systematized ideas of persecution (toxic psychosis)	Infected teeth, 29	Tonsils infected	Tonsillectomy and 29 teeth extracted	Discharged in 5 mos.; economically independent; well for 3 yrs.	Two wks. after completion of dental and tonsillar work the psychosis ceased.
5 5484 F. 18	Pain in head (toxic psychosis); duration, 2 yrs.	Upper right molar and 2 other teeth infected; severe infection of right antrum	Tonsils infected	Tonsillectomy; rt. antrum opened, curetted; pus sac removed	Marked improvement, but not yet normal; 6 mos. since detoxication	Mental status indicated early dementia precox; removal of infection has arrested the psychosis.
6 5150 M. 56	Insomnia for 20 yrs.; early mental disorientation	Severe necrosis of left upper jaw surrounding devitalized molar; severe infection of left antrum	2 teeth removed, bone curetted; the antrum opened and drained	Weight increased; sleeps very well; mentally keen 1 yr. later	Duration of jaw infection at least 20 yrs.
7 5158 F. 44	Shortness of breath; gas; impaired vision precipitated by pregnancy 6 yrs. ago; headache constant and severe	Eight infected teeth found in 1923	Infected tonsils found in 1919; usual signs of a chronic nephritis and cardiovascular deterioration; systolic, 175, diastolic, 110	Tonsillectomy in 1919 and 8 infected teeth removed in 1923	No marked improvement in symptoms; cessation of all subjective symptoms; restoration to active life	Never sick until acute nephritis in 5th mo.; induced labor saved her life, but nephritis continued; removal of tonsils alone insufficient to arrest deteriorative processes; points to necessity of removing all oral foci.
8 4653 M. 61	Headache; pain in both eyeballs; loss of sense of smell; "belly aches"; constipation; neuritis; cardiac arrhythmia	Serious infection of rt. upper jaw; infected root in rt. antrum; sclerotic and infected	Hemorrhoids; pericolitis at splenic flexure; obstructive constipation	Surgical removal of oral infection; hemorrhoidectomy	Greatly improved	Abdominal and cardiac symptoms shown to be secondary to oral and anal involvement.

9	3893 F. 40	Rapidly increasing blindness; severe orbital pain	Edentulous; throughout life a severe dental infection; double maxillary sinusitis; chronic ethmoiditis	Double glaucoma; para-central scotoma and cupping of disk of rt. eye; no intranasal pathology	Both antra opened, curetted and drained; infection was severe; double iridocyclitis	One yr. later, permanent decrease in tension; intercurrent myopia disappeared in 3 mos.; pain ceased in 4 mos.	Chronic intestinal invalid for 20 yrs.; improved by hemicolectomy 10 yrs. ago; total colectomy 3 yrs. ago; if infection caused eye lesions it began in teeth.
10	3987 F. 64	Chronic eye trouble 3 yrs.; total blindness of left eye 1 mo.; right eye nearly blind; severe nausea, vomiting and abdominal pain	Edentulous for 30 yrs.; maxillary osteomyelitis and necrosis; double maxillary sinusitis	Chronic uveitis; iridocyclitis; vision: O.S., 0; O.D., 29/200	Necrotic bone removed; both antra were opened by oral route, curetted and drained	Three days later able to distinguish buildings; in 3 wks. able to read 4th line of optic chart; in 1 yr. able to read ordinary print with right eye; left eye blind; abdominal symptoms improved	Important association of gastrointestinal and eye conditions and improvement in both; patient has gained 30 lbs. and for 3 yrs. past has been able to read and do all her own housework.
11	4026 F. 64	Arthritis and cholecystitis 10 yrs.; greatly disabled; hands nearly useless; in autumn of 1922, sudden pain, redness and diminished vision of left eye; nearly absent 4 days after onset	In 1921 dental infection found; relayed; upper left 3d molar infected; severe left maxillary sinusitis and ethmoiditis	Almost constant pain and tenderness over gall bladder in 1922; iridocyclitis of left eye	Tonsillectomy in 1919 and 13 teeth were removed 1921; 3d molar removed; left antrum curetted and drained; later right antrum curetted and drained	Arthritis checked; G.I. symptoms slowly increasing; vision restored 1 mo. after antral drainage; great improvement in G.I. symptoms	Bad surgical risk prevented cholecystectomy; right tonsil drained into right axillary lymphatics; important relationship between all mental symptoms and oral infections.
12	5368 M. 70	Rapid and increasing loss of vitality; insomnia and headache; mental depression; pain in leg; Dupuytren's contracture of rt. ring finger 15 yrs.	Pyorrhea; severe periodontal infection of both upper molar areas; severe double maxillary sinusitis	None	Infected teeth were removed; both antra opened orally, curetted and drained	Almost immediate disappearance of pain in leg; general health better; relaxation of Dupuytren's contracture	Symptoms arrested for 9 mos. recurrence of sinus infection and some symptoms; interesting relationship between oral infection and Dupuytren's contracture.
13	5627 F. 73	Severe diarrhea; duration, 4 mos.	Six devitalized teeth; severe periodontal infection	Tonsils infected; 3d degree colitis with fibrosis	All dental and alveolar infection eliminated	Improved; occasional attacks of diarrhea	Each extraction followed by severe prostrating diarrhea.
14	5569 M. 39	Neuritis; spasmodic severe pain in left shoulder 4 wks.; sleeplessness; frequent disability both arms 10 yrs.	Devitalized infected upper and lower molars; sinuses negative	Colon stasis, 72-hr. total; tonsils out; w.b.c., 6800; polys., 23 per cent; lymphs, 72 per cent	Dental infection eliminated	Greatly improved after 2 mos.; sleeping normally; able to play	Elimination baths and electrothermic treatments made pain worse; severe blood-count inversion; roentgen-ray of shoulders negative.
15	5220 M. 20	Fatigue, mental and physical irritability; personality deterioration	Two impacted 3d molars; lower angle of left antrum sclerotic	Infected tonsil stumps; trace of albumin; no casts; renal function, 75 per cent; 3 hrs.; cardiac hypertrophy; mitral insufficiency; blood-pressure, 175/125	Tonsil stumps were removed; impacted 3d molars removed	Marked physical and mental improvement; able to work on farm; blood-pressure 145/90	Important example of marked personality change in youth associated with extensive oral infection; had been high-grade scholar, now 3d-grade; permanent mental, moral and physical deterioration.
16	3924 M. 53	Severe attacks of pain in upper right abdomen; nausea, vomiting; acutely ill 6 wks.; indigestion 4 yrs., with jaundice, headache and loss of strength	February, 1921, 2 infected teeth and 2 areas of osteomyelitis; infected left antrum	Typical gall bladder tenderness	Two infected teeth removed; surrounding bone curetted; antrum curetted and drained	Gained 25 lbs. in 8 mos.; cessation of all abdominal symptoms	This patient would have been operated on for gall bladder had he not been a poor surgical risk; shows important relation of oral infection to abdominal lesions.

In attempting to explain this apparent inversion of the normal ratio between the cellular constituents of the blood, close scrutiny of all figures is necessary. The ratio between the polymorphonuclear neutrophils and the total lymphocytes seems to indicate a decrease of the former and an increase of the latter. What occurs, however, is this: There has been an actual loss in cellular components, as shown by the total cell counts for the two groups. It is a fact, however, that, whereas the *percentage* of lymphocytes has changed, their *total number* is the same for both groups—while the

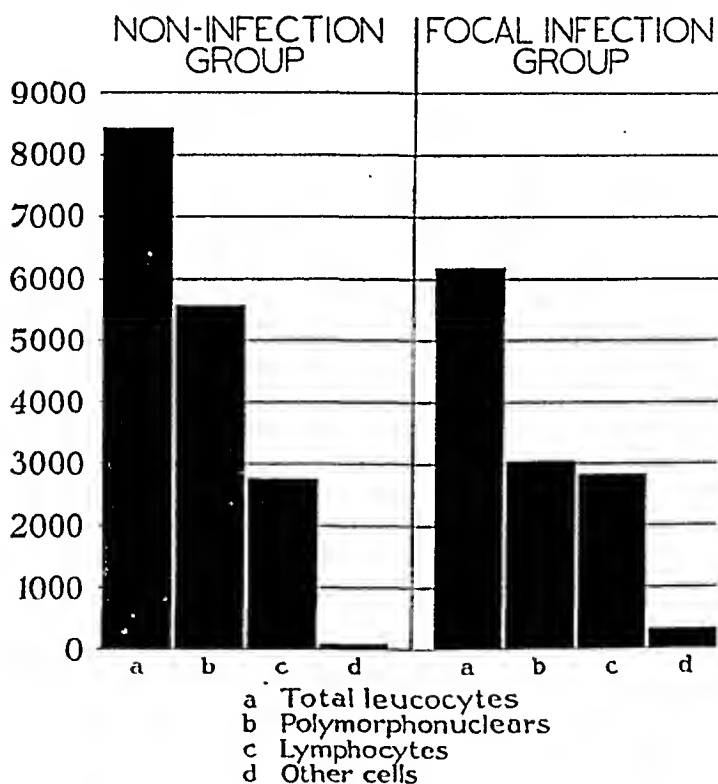


FIG. 2.—Chart showing average white-cell count of 44 adults not presenting evidence of focal infection, and of 35 adults presenting definite evidence of focal infection. Note (1) the decrease in total white cells in the focal-infection group; (2) the corresponding decrease in the polymorphonuclear cells, and (3) the absence of change in the lymphocytes.

total number of polymorphonuclear neutrophils is decreased in the focal-infection group by an amount approximately equal to the difference between the total cell counts of the two groups. It is evident then, from these figures, that alterations in the blood picture of the focal infection group as a whole must be due to changes affecting chiefly if not entirely the polymorphonuclear neutrophile cells. (This is graphically shown in Fig. 2.) Just as in the acute febrile infections there is an increase in these defensive phagocytes, so in the chronic non-febrile infections there is finally

a marked reduction in their number. With constant extensive leukocytic infiltration about chronic infective foci, a point is reached where cell destruction exceeds cell regeneration. After reduction of the toxemia by mechanical means there is a definite tendency for the cellular ratio to return to normal.

Finally, in discussing the chart analysis of 16 patients (see Table), all suffering from remote and general pathological conditions due chiefly to oral infection, we would call especial attention to the following: (1) To the three instances in which blindness was considered by competent oculists to be imminent and in which the progress of the lesion was arrested by oral detoxication; (2) to

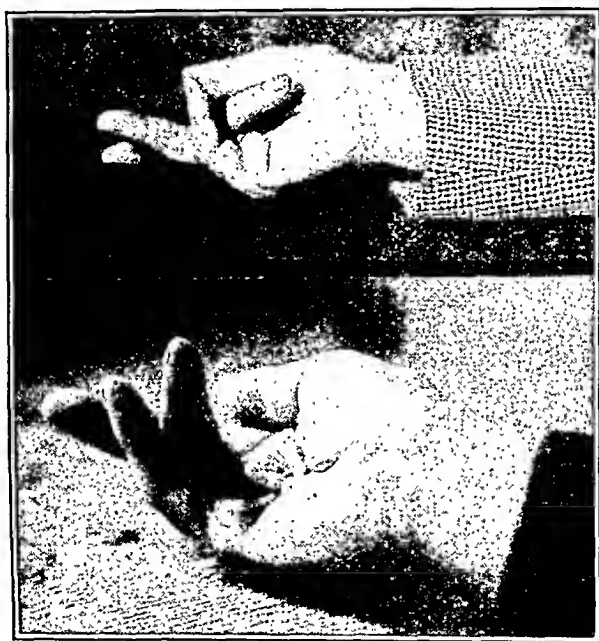


FIG. 3.—Showing relaxation of Dupuytren contracture eight months after oral detoxication.

3 patients in whom cardionephritic lesions predominated; (3) to 2 patients in whom insomnia was the chief complaint; (4) to 2 patients suffering from well-defined psychoses; (5) to 4 patients presenting typical symptoms of gastrointestinal invalidism and who obtained subjective relief from oral detoxication; (6) to two patients suffering from neuritis, definitely arrested by the same procedure. An interesting observation upon one patient, No. 5368, consisted in the unexpected but definite relaxation which took place in a Dupuytren contracture of fifteen years' standing (Fig. 3).

On all hands the evidence appears to be increasing that dental infection stands in an important and until recently unrecognized causal relationship to many remote systemic pathological conditions.

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REVIEWS.

THE CURE OF PULMONARY TUBERCULOSIS BY REST AND EXERCISE.
By HUGH M. KINGHORN, M.D. Pp. 169; 8 illustrations. Boston:
Richard G. Badger, 1924.

THIS small volume deals with the rest treatment of tuberculosis in an interesting manner. There is a well-written account of the work of three pioneers in the treatment of tuberculosis, Brehmer, Dettweiler and Trudeau, which brings in the personality of these men in a way that makes this book really entertaining. A discussion of methods and results of treatment refers to the work of Paterson and Joseph Pratt. This book is well written, the subject briefly but thoroughly covered in a sound manner.

R. T.

CONTRIBUTIONS FROM THE PEKING UNION MEDICAL COLLEGE.
Vol. III. Pp. 495; numerous illustrations. Peking, 1924.

THE thirty-eight articles making up this volume are ample evidence of the good work that has been done at Peking since the appearance of the second volume of contributions in 1922. Most prominent are the biochemical papers by Read, Wong and Wu, together with the important article on gas and electrolyte equilibria in the blood by van Slyke, Wu and McLean. Two papers by Detwiler on spinal cord experiments in *Amblyostoma* are also noteworthy. The formist will regret that the back of each of the three volumes differs from the others.

E. K.

ANATOMISCHE PRÄPARIERÜBUNGEN. By HANS VON VIRCHOW,
Vol. I. Cloth: Price, Marks 4.00. Pp. 66; 13 illustrations.
Vol. II. Cloth: Price, Marks 5.50. Pp. 110; 13 illustrations.
Berlin and Leipzig: Walter de Gruyter & Co., 1924.

THESE two little dissecting manuals are from the pen of a well-known anatomist, who embodies in the text the methods used in

his institute. The booklets are intended as a guide for the student while he is actually at work. The contents are logically arranged, the descriptions clear and to the point; many "remarks" indicate the practical applications. While Professor Virchow's books will no doubt be well received by students in German Universities, there are so many excellent dissecting guides in English that a new work on this subject would have to be of exceptional merit to supplant those in use in American schools. B. L.

THE CHEMISTRY OF THE BLOOD IN CLINICAL MEDICINE. By O. L. V. DE WESSELOW, M. B., F.R.C.P., Chemical Pathologist and Physician to Out-Patients, St. Thomas's Hospital, London. Pp. 255; 12 illustrations. London: Ernest Benn Limited, 1924.

THIS is the most satisfactory book on this subject from several points of view which the reviewer has had the pleasure of seeing. For the practitioner who desires a brief, clear statement of the chemical aspects of blood chemistry, this book can be heartily recommended. For the teacher of biochemistry in the medical school who has little contact with the clinical problems of the practitioner this book will serve as a reminder of the practical applications of the science which he is teaching. In the 255 pages of the book there are included chapters on each of the important phases of the chemistry of the blood; first the chemistry of the normal blood and then a consideration of the changes which occur in diabetes, nephritis, acidosis, alkalosis, hyperemia, etc. Especially is the chapter on acidosis clear, concise and eminently sane. One might perhaps find fault with the use of the old CO_2 capacity method as described but other than this no possible criticism of the book can be made. O. P.

THE EXTRAORDINARY EXPLOITS AND EXPERIENCES OF MUNCHAUSEN, M.D. By JULIAN WALTER BRANDEIS, M.D. Pp. 229; numerous illustrations. The Quip Publishing Company, 1924.

A RATHER dismal attempt to apply Munchausen with a dash of Mark Twain to modern medicine. Hypnosis-anesthesia, endocrinology, psychoanalysis, eugenics, cancer cures and similar topics are trotted out only to show very halting paces. Munchausen's self-rescue from a deep chasm by picking the fruit of the Pissepewa tree on which he was suspended and the general practitioner's device for preventing his practice from falling into the hands of the specialist are welcome though small oases in the arid desert. The illustrations are about as good as the text. E. K.

DEVELOPMENTAL ANATOMY. By LESLIE B. AREY, Professor of Anatomy at the Northwestern University Medical School, Chicago. Pp. 433; 419 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

UNDER the above title, we have a new presentation of the Prentiss text-book of embryology, of which Professor Arey was editor and co-author for some years. He has virtually rewritten the book, has rearranged the order of the various topics, and has made minor additions to bring the information up to date. The dissection of the pig embryos, ranging in size from 5.5 mm. to 35 mm. remains as one of the unique features of the book. The use of these dissections has added greatly to the interest of embryology as a laboratory science, and serves to render concrete certain developmental processes. As a well-written and well-illustrated text-book, it will meet with continued success under Professor Arey's authorship.

W. A.

REGENERATION FROM THE PHYSICOCHEMICAL STANDPOINT. By JACQUES LOEB. Late Member of the Rockefeller Institute for Medical Research. Pp. 143; 115 illustrations. New York; McGraw-Hill Book Company, 1924.

THIS was one of the last works from the experimental laboratory of Jacques Loeb, the eminent biologist. Using the plant *Bryophyllum* of the Bermudas, he studied why mutilation or wounding of an organism gives rise to phenomena of growth which do not occur without mutilation, and why the new growth frequently results in some kind of restoration of the old form. He was able to show a quantitative relation between the mass of the original plant substance and the mass of the regenerated part. The work lies in the domain of general physiology, and is one of the first attempts at a quantitative investigation of the phenomena of regeneration.

W. A.

ZEITSCHRIFT FÜR MIKROSKOPISCH-ANATOMISCHE FORSCHUNG; Vol. I, Parts 1 and 2; PROF. H. STIEVE, University of Halle, Editor. Pp. 351, 6 plates and many text figures; Akademische Verlagsgesellschaft M. B. H., Leipzig, 1924.

THE condition of scientific periodicals in Germany for the last few years has been a matter of considerable interest. Certain journals have been discontinued, others have joined forces, considering it better to continue as one successful journal than as two struggling under difficulties. At the present time fresh activity is observable, and among the new journals resulting is the above-

named one. The desirability of having a new journal for histology has come about through the amalgamation of the *Archiv für Mikroskopische Anatomie* with Roux' *Archiv für Entwicklungsmechanik*. The resulting journal, under the editorship of Roux, contains articles on biological topics, mainly experimental in nature. The *Archiv für Mikroskopische Anatomie* was for sixty years the place of publication of the most noteworthy researches in histology, and as the character and identity of this journal has been lost by its union, there came the need for a journal of similar content and scope. In the two parts of the new journal which have appeared there are ten articles, of which four are from the editor's own laboratory, and all of great interest. There are eight assistant editors, representing well-known anatomical centers such as Utrecht, Berlin, Zurich and Upsala. One may safely predict a successful future for this new contemporary.

W. A.

THE MEDICAL RECORD VISITING LIST OR PHYSICIANS' DIARY FOR 1925. Pp. 300. New York: William Wood & Co.

THIS useful pocket notebook is designed for recording visits, charges, etc. The first few pages contain tables of dosage and other miscellaneous data.

J. A.

PRACTICAL LECTURES, DELIVERED UNDER THE AUSPICES OF THE MEDICAL SOCIETY OF THE COUNTY OF KINGS, BROOKLYN, NEW YORK. (1923-1924 Series.) C. A. GORDON and T. S. WELTON, EDITORS. Pp. 484; 135 illustrations. New York: P. B. Hoeber, 1925.

THE Kings County Medical Society, wishing to celebrate its one hundredth anniversary by a demonstration of public service, decided to arrange a series of practical lectures on topics chosen by its committee, "believing that continuous education of the practising physician would be the greatest possible contribution that the Society could make in the cause of public health." The twenty-five lectures were so successful that it was thought advisable to publish them. The surgical and obstetrical topics predominate—the "surgical abdomen" (eheul), surgical diagnosis, appendicitis and similar topics are presented by such well-known men as Blake, Deaver and Polak. Medical topics—such as renal function, chronic arthritis, bacterial endocarditis and epidemic encephalitis are covered by Mosenthal, McCrae, Libman, Tilney and others, with one lecture each on common skin diseases by Fordyce; every day bacteriology by Oliver; rational pathology by Ewing, and medical psychology by Walsh.

E. K.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Antirachitic Properties Imparted to Inert Fluids and to Green Vegetables by Ultraviolet Irradiation.—Following up the recent lead obtained when it was discovered that ultraviolet irradiation of cod-liver oil increased its antirachitic property, HESS and WEINSTOCK (*Jour. Biol. Chem.*, 1924, 62, 301) now report similar studies on a variety of substances and foods. Such inert fluids as cottonseed and linseed oils become active antirachitic agents after irradiation *in vitro*, and they retained this property for a considerable period. Wheat grown in the dark was valueless in this regard, but when grown in sunlight or irradiated with ultraviolet light it was strongly protective. Vegetables irradiated, either before or after being plucked, showed a very marked increase in their antirachitic property. This would definitely point to the uselessness of green vegetables grown under glass in winter as sources of protection against deficiency diseases.

Modification of Diphtheria Toxin by Formaldehyde.—GLENNY and HOPKINS, in 1923, first showed that diphtheria toxin could be so modified by the action of formaldehyde that the specific toxicity was greatly reduced while the binding power for antitoxin remained unchanged. The present paper by GLENNY, HOPKINS and POPE (*Jour. Path. and Bacteriol.*, 1924, 27, 261) deals with further details of this formalization and the use of this altered toxin for immunization. The amount of formaldehyde required to render a given toxin preparation nontoxic depends greatly on the amino-nitrogen content, as was to be expected, since this is where the bulk of formaldehyde goes. Such nontoxic toxin may have its total combining power for anti-

toxin little affected, but the speed of this combination is greatly lessened. By acid precipitation of the altered toxin they were able to obtain as much as a forty-fold greater combining capacity for antitoxin in comparison to the amount of amino-nitrogen present. This concentrated formalized toxin they found to be far superior to ordinary toxin for active immunization against diphtheria and in the commercial production of antitoxin. The immunity to the disease appears earlier (in rabbits as early as nine days, in guinea-pigs eleven days) and is of a high degree.

Immunological Significance of Vitamins.—In their earlier work WERKMAN, BALDWIN and NELSON failed to account for the decreased resistance to infections in animals on a deficiency diet on the basis of altered antibody production or reduced bactericidal power of the blood. They did find a lowered body temperature and reduced phagocytosis in these animals, and thought these findings of some significance. They have now (*Jour. Infect. Dis.*, 1924, 35, 549) studied the effect of a deficiency diet (B vitamin) on the resistance of rats to diphtheria toxin. They found an increase in the susceptibility of the rats to the toxin, death following the injection of doses much below the lethal amounts for rats on normal diets. Even with this susceptibility the rats did not show a lowered antitoxin production. The principal cause of the greater toxicity for these avitaminic rats lay in the effect of the toxin on the blood pressure. A marked and sudden drop in pressure occurs usually on the second or third day after the injection, and is progressive until death intervenes. A mere lack of vitamin B alone serves to cause a progressive fall in blood pressure. The increased susceptibility to diphtheria toxin apparently lies in its augmentation of this already abnormal state.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Common Duct Stones and Primary Suture of Common Duct.—ELISCHER (*Centralbl. f. Chirurgie*, 1924, 49, 2690) says that suturing the common duct is contraindicated only in the brittle, thin-walled type of common duct. This procedure was followed in 16 selected cases in a series of 86 cases of stones in the common duct. In the remaining 70 cases drainage and palliative operations were performed. Thirteen persons in the series of 16 gave history of jaundice, while all showed bile in urine at time of operation. Seven showed fever at time of attack.

The stones were solitary stones in 14 patients, 7 were incarcerated in the region of the papilla, while 7 were movable. One case showed 2 stones, while the remaining case showed several faceted stones. There were 2 tiers of sutures and a fine capillary drain was carefully inserted alongside. The author stresses the fact that drainage and short circuiting operations should be used in strict emergencies—while the procedure described should be used in carefully selected cases.

The Effect of Ligation of Branches of the Renal Artery.—BELT and JOELSON (*Arch. Surg.*, 1925, 10, 117) say that the changes produced in the circulation of the kidney following ligation of one of the larger renal arterial branches are closely portrayed by means of the celluloid injection method. An almost absolute ischemia confined to the region supplied by the blocked vessel is followed by a late ingrowth of small anastomatic channels into the bloodless area. These increase in size up to the fifth week, after which time scar-tissue formation, resulting from the effects on the stroma of the long period of ischemia, again makes the area relatively avascular. The end-result is a depressed stellate scar equal in area to the region supplied by the ligated branch. The clinical significance of this is self-evident. Although in renal surgery it may at times be necessary and justifiable to divide one of the large branches, it should be borne in mind that such a procedure causes a necrosis of the area of renal parenchyma supplied by that vessel. While this necrosis may not be of a magnitude which will result in clinical evidence of renal insufficiency, still it does definitely decrease the amount of renal reserve tissue, for restoration of function in such areas is shown to be anatomically impossible.

Postoperative Massive Collapse of Lung.—SCOTT (*Arch. Surg.*, 1925, 10, 73) states that postoperative massive atelectasis presents a striking clinical syndrome and is relatively frequent. It is differentiated from all other acute conditions by displacement of the heart and mediastinum toward the side that shows evidence of pulmonary consolidation. Asymmetry of the chest, unilateral limitation of respiration and cyanosis are early and striking signs. Latent cases occur, which are nearly symptomless and others are so severe that they resemble pulmonary embolism. The prognosis is excellent. Massive atelectasis may be complicated by bronchopneumonia and in this group the fatalities occur. The mechanism of massive atelectasis appears to be a reflex blocking of the finer air passages in the affected lung tissue, quite possibly of vasomotor origin. Collapse of lung tissue after operation seems to be a significant element in other pulmonary complications.

The Surgical Treatment of Paralytic Deformities of the Foot.—MAYER (*Amer. Jour. Surg.*, 1924, 38, 289) believes that first progress in treatment of these deformities came in tendon transfer. Further improvement was made by operations, dealing with reconstruction of the bones of the foot. Whitman's operation of astraglectomy, combined with posterior displacement of the foot, gives a suitable foot even when most of the muscles of the calf are paralyzed. It has, however, the disadvantage of shortening the extremity from $\frac{1}{2}$ to 1 inch. G. G. Davis advocated a subastragaloid arthrodesis combined

with a posterior displacement of the foot. Michael Hoke published a stabilizing operation in 1921. His operation reshapes the head and neck of the astragalus in such a way as to overcome the deformity and arthrodeses the joints between the astragalus, scaphoid and os calcis so as to maintain the bony relationship in any position that the surgeon desires. In milder forms of flat-foot, there is weakness of the tibialis anticus muscle, but the other invertors of the foot are strong enough to prevent the development of marked deformity. This type alone can be improved by non-operative measures. Outspoken paralytic flat-foot, paralytic club-foot and paralytic calcaneocavus are treated by various combinations of tendon transference with stabilizing operations upon the bones of the feet. The author stresses careful grading of the deformity according to the muscles paralyzed and the degree of deformity. In very mild cases non-operative measures were sufficient; in the moderate grade tendon transference was done; in the more marked cases tendon transference was combined with bone reconstruction.

Surgical After-Treatment in Thyroid Disease.—DEAVER (*Amer. Jour. Surg.*, 1924, 38, 296) says that every means of treatment known to be of real value in the postoperative care of thyroid cases should be available for reference when needed. Operative mortality in goiter work may be lowered by individualizing every case. The patient's resistance should be at the highest available point. Obesity, excessive summer heat, great loss in weight, a rapid pulse, which will not slow down under rest, but rises quickly on the slightest exertion, are danger signals, even with a low metabolic rate. Five things are essential in every operative goiter case. They are rest of body and mind, a reconstructive diet, sufficient elimination, free ingestion of fluids and carefully directed medication. Iodin aside from its use in simple and adolescent goiter, may, according to Plummer, have a special indication in the exophthalmic form, either before or after operation or both. Postoperative simple goiter usually runs a quiet course. The exophthalmic type may manifest a rather varied reaction merging from a mild form into that which is stormy or even violent. Water should be given from the start, regardless of vomiting. Cerebration must be subdued and renal function encouraged. Cold externally is often of great value. Of drugs, the most important are luminal, bromides, morphin, digitalis and in selected cases, iodine. Collapse of the wind-pipe and grave secondary hemorrhage are the tragedies of goiter surgery. Recurrence in simple goiter may be compensatory in young persons, and may therefore subside. If it persists, medical or surgical treatment is advised. Recurrence in the toxic or exophthalmic form, calls for further removal as a rule. The advanced exophthalmic case with fixed complications cannot be completely cured. Every operative goiter case, simple or toxic, should be kept under observation until the best possible results have been reached. Advice and treatment from too many sources should be discouraged.

Malignant Epithelial Tumors of the Thyroid.—GRAHAM (*Surg., Gyn. Obstet.*, 1924, 39, 781) declares that at least 90 per cent of malignant tumors arising from thyroid epithelium have their origin in preëxisting

adenomata. The morphological character of the cells and tissue is an unreliable basis for the determination of malignancy of thyroid epithelial tumors. The malignancy of thyroid epithelial tumors depends upon their tendency, or capacity to invade the capsule, surrounding tissue, lymphatics or bloodvessels. The most constant single indication of thyroid epithelial malignancy is invasion of the bloodvessels. Scirrhus and papilliferous adenocarcinomata are the only two types of epithelial malignancy in which invasion of the bloodvessels has not been observed. Epithelial tumors that are encapsulated are benign, irrespective of their microscopical appearances otherwise. Epithelial tumors, in which one finds invasion of the bloodvessels cannot be regarded as entirely harmless, irrespective of their microscopical appearances. The term carcinoma is proper for epithelial tumors of the thyroid that are malignant, regardless of their microscopical appearance. The term malignant adenoma is useful and convenient for the purpose of denoting a subgroup under carcinoma.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

NEW YORK.

Treatment of Asthma with Autogenous Vaccines.—THOMAS and TOUART (*Arch. Int. Med.*, 1924, 34, 79) report the results obtained in the treatment of 62 cases of asthma by means of autogenous vaccines. Treatment was based on the results of reactions to intracutaneous tests with autogenous vaccines after preliminary routine tests for sensitization to foreign proteins had been made, and surgical treatment given to those cases which showed abnormalities of the nasopharynx, nasal sinuses, tonsils or teeth. The important factors in the use of vaccines were: (1) Proper selection by the intracutaneous test; (2) preparation of each organism in a separate vaccine; (3) the use of a therapeutic dose just sufficient to produce a mild local reaction; (4) adherence to this dose so long as it continues to produce such a reaction; then increasing it; (5) frequent dosage early in the treatment with a gradually lengthened interval, followed by (6) prolonged administration at relatively long intervals. The method of testing with autogenous vaccines described by THOMAS, FAMULENER and TOUART (*Arch. Int. Med.*, 1924, 34, 85) depends on a standardization of vaccine based on the HOPKINS method (*Jour. Am. Med. Assn.*, 1913, 60, 1615) in which a 1 per cent suspension in physiological sodium chlorid solution is prepared from the measured packed bacterial residue, and composes the stock vaccine. A unit consists of that amount of bacterial substance which is present in 0.01 cc of a 1 per cent suspension, and this quantity has been found to be the most favorable amount to produce a skin reaction when applied intradermally in a sensitive patient. Positive reactions may appear within ten to thirty minutes or in twelve hours and persist from two to

five days. Test vaccines were made from organisms isolated from tonsils, nasal sinuses, pharynx and stool. Treatment vaccines were prepared from the stock vaccine and contained approximately 1,000,000,000 organisms per cc. The initial dose was 100,000,000 organisms of each type selected. If a local reaction occurred it was repeated at intervals of two or three days until none followed. Then the dose was doubled on each injection until the desired result was obtained. Seldom did the dose exceed 400,000,000 organisms. With improvement in symptoms the interval between injections was increased first to five, later to seven days. Weekly, bi-weekly, or monthly injections were given after relief of symptoms and physical signs occurred because of the tendency to relapse. Of the 62 patients treated 53 have been either completely relieved or materially improved.

The Question of the Practical Significance and the Treatment of Extrasystole.—In the great majority of cases cardiac extrasystole is not dependent upon organic changes of the heart muscle, but is a functional disturbance of the heart. In most cases the prognosis is favorable, and SCHULTZ (*Deutsche med. Wchschr.*, 1924, 40, 1357) emphasizes the importance of determining by the electrocardiograph whether the cardiac irregularity is due to extrasystole or is a perpetual irregularity of the heart due to auricular fibrillation. He summarizes briefly the various opinions of eminent heart specialists, and their choice of treatment. Digitalis is usually of no use although small doses are sometimes beneficial aside from its effect as a general tonic. Other physicians use quinin and quinidin both of which substances cause a diminution of cardiac irritability. For the large majority of cases no medication is indicated, but elimination of deleterious influence and cure of insomnia.

A New Diet for Peptic Ulcer.—COLEMAN (*Jour. Am. Med. Assn.*, 1924, 83, 885) reports a new diet for peptic ulcer which has been used for twelve years and given satisfactory results. Fat is given in the form of olive oil or unsalted butter, protein is supplied by egg white, and carbohydrate by rectal enemata of glucose solution. At the onset of treatment the patient is put to bed, the alimentary tract cleaned out by castor oil or some other laxative, and for from three to five days no food is given by mouth. Water is supplied by the enemata, and if these do not control thirst 1 to 3 ounces of water at room temperature may be given by mouth. After a daily enema of soapsuds 300 cc of a 10 per cent glucose enema is given by the drip method and repeated two or three times during the day. On the fourth to sixth day feeding by mouth is begun. One and a half to 2½ ounces of chilled olive oil alternating with the whites of 3 to 4 eggs every two hours is given the first day, increasing to a maximum of 150 cc of olive oil and 6 to 8 egg whites daily. To those patients who are unable to take olive oil unsalted butter, egg-yolk or cream in corresponding amounts may be given. That is 6 ounces of butter equals 5 ounces of olive oil or 2½ ounces of cream. Eight grams of salt are given in the food daily to prevent loss of chlorine from the body. This diet is continued for three to four weeks and for many months afterward only specially selected foods are given. The object and advantages of this diet is to give foods which do not incite gastric secretion and which least stimulate the

motor activity of the stomach. Gastric distress subsides quickly after treatment is begun, and in no instance was it necessary to give drugs to accomplish this result.

Autoserotherapy in Pleural Effusion.—MARCOU-MUTZNER (*Monde méd.*, 1924, 653, 600) advocates autoserotherapy in pleural effusions as first used by Gilbert of Geneva rather than thoracentesis with artificial pneumothorax. The former method he has used successfully for twenty years in every case of pleurisy with effusion whether tuberculous or not, and has seen no bad effects. After 2 or 3 injections of serum there is a marked diuresis and disappearance of the effusion. He has never seen a cold abscess develop, but does not approve of reinjection of pus, although clear or bloody fluid may be reinoculated. At the site of puncture without withdrawing the needle from the skin 2 cc. of pleural fluid is reinjected subcutaneously. This procedure is repeated every two days, and after a mild reaction there follows a marked diuresis, feeling of well-being, with diminution of the exudate. The greater the effusion the more rapidly one obtains beneficial results, and in the long-standing cases results are less marked than in the recent cases.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Significance of the Presence of the Nephrogenic Zone of the Kidney in the Normal and the Syphilitic Fetus and the Newborn.—MEBANE.—(*Am. Jour. Dis. Child.*, 1924, 28, 668) made histological studies of the normal kidney in 162 fetuses and newborn infants, and he found that the development of the renal tubules is completed when the infant is between 45 and 48 cm. in length. At birth in the full-term infant, which is from 48 to 52 cm. in length, the growth zone, or nephrogenic zone, of the kidney is absent. The nephrogenic zone is usually absent when the weight of the dead fetus is more than 2500 gm. The study of the kidneys in 14 patients with congenital syphilis failed to show in a single case a retardation in the development of the kidney with a persistent nephrogenic zone. In congenital syphilis, the nephrogenic zone disappeared at the same time as it did in the control series, when the infant was between 45 and 48 cm. in length. The presence of the nephrogenic zone is almost certain evidence of prematurity. Its prominence, whether slight, moderate or marked, may give some idea of the age of the fetus.

Endocrinology in Pediatrics, with Special Reference to the Hypoplastic-Dyspituitary Type of Child.—DOWD (*Arch. Ped.* 1924, 41, 801) reports a number of cases, and comments that persons of all ages may be

abnormal or inadequate because of glandular deficiencies. Children of the status thymico-lymphaticus type, frequently overweight, sometimes tall, slender and loose-jointed, are a difficult problem of adjustment. The nature of their growth and development renders them frequently self-conscious, inadequate, prone to injury, and with a low resistance to infection. They can be assisted more rapidly to a condition of normality by a study of their internal secretions, with the administration of the appropriate glandular extracts, than by neglecting these glands and relying entirely on measures relating to diet and hygiene and correction of physical defects. Even the cretins are not the simple case of thyroid deficiency that they have always been considered. They are hypoplastic and their trouble is a pluriglandular one. Such conditions as epilepsy have some relationship to disturbance of internal secretion that warrants further study. Pituitary extracts have a distinctly favorable influence on fatigue, and on such symptoms as headache and bed-wetting when used in proper amounts and can aggravate the condition if overdose is given. Caution must be observed in the use of glandular extracts. Thyroid should be used in small doses, while pituitary whole gland and the anterior lobe extracts can be pushed unless the headache ensues, which was previously absent, or the existing one is aggravated. In some cases the enuresis will be aggravated rather than improved if too much extract is given. In the addition to the administration of these extracts by mouth, they may be given by injection with benefits in selected cases. Ovarian and testicular extract are useful when puberty is delayed. Large doses of pituitary extracts are not indicated when the sella is small and enclosed, or severe headache will follow. Rest periods when dosage is omitted are necessary from time to time. It is a temptation for the user of gland therapy to believe it to be the proper method of therapeutics in all kinds of cases. Such a feeling is unfounded. A great deal of good can be done by this treatment with the proper selection of the case, dosage and frequency of administration.

Residua and Sequelæ of Epidemic Encephalitis.—GOODHART and COTTRELL (*Jour. Am. Med. Assn.*, 1925, 84, 32) says that human intelligence, comprehending the activity of the mind as a whole, includes the capacity of reception, assimilation and criticism. It is biologically dependent in large measure on the gray mantle of the brain. The emotions, strictly speaking, are referred to for their physical components to parts of the subcortical level, thalamus and corpus striatum, and are probably associated with both conditional and unconditional sensorimotor reflexes. When one considers the graduated disturbances of intellect and emotion that have appeared so strangely associated in postencephalitis and have affected attention, the higher sensations and the higher psychic combination processes, including those of critical judgment, imagination and creative power, it is a fair ground for assumption that all of these faculties are associated with the same brain segments that are functionally the seat of emotional reactions. The further painstaking investigation of encephalitic patients may yet give us information as to the function of the subcortical brain segments, and furnish valuable biological data with respect to the emotions and the higher creative processes. They analyze a series of cases. In a

study of the static, kinetic and synergistic mechanisms affected in encephalitis, and in such classified entities as chorea, dystonia musculorum, striatal syndromes, paralysis agitans and multiple sclerosis, not only is it indicated that the damaged nerve centers are the same anatomically, but also it is suggested that the acute pathologic condition in the one case terminates in a histopathologic process which is the same in the chronic stages of encephalitis as in the conditions that obtain in the syndromes of older nomenclature. A review of histories and observations does not suggest a more or less constant relationship between the symptoms of the acute illness and the development later of a particular type of motor deficiency.

A Study of the 1923 Epidemic of Anterior Poliomyelitis in Kansas.—DIVELEY (*Jour. Am. Med. Assn.*, 1925, 84, 85) made studies of the data of the antero-poliomyelitis epidemic. If an early diagnosis is made and proper treatment instituted during the febrile stage, the resulting cord involvement is not only lessened, but in a great measure prevented. If proper treatment is carried out during the second or convalescent stage, from 75 to 85 per cent of the cases show marked improvement or complete recovery, against 40 to 45 per cent of partial recovery if proper treatment is not carried out. If proper treatment is carried out during the first and second stages, fully 90 per cent of the deformed limbs and backs can be prevented. Many cases recover spontaneously without treatment, while others still show signs of paralysis after one year of careful supervision. There are definite anterior poliomyelitis carriers. The infection is selective, and may run through neighborhoods or families, picking out various individuals. Most persons in a community during an epidemic have the disease in the light or abortive form, which gives immunity.

The Dick Test and Active Immunization with Scarlet Streptococcic Toxin.—ZINGHER (*New York State Med. Jour.*, 1924, 24, 915) regards the Dick test as being a reliable method for determining susceptibility and immunity to scarlet fever. In his experiences with the test in more than 7700 cases, 8 positive reactors and none of the negative reactors have developed scarlet fever. The rapid appearance of the reaction in from eight to twelve hours is of great clinical value for this purpose. The Dick test helps in the diagnosis of doubtful cases of scarlet fever. In 232 cases of scarlet fever the Dick test showed that 91.3 per cent gave positive reactions during the early stages of the disease and negative reactions during convalescence. There were 19 patients who gave a persistent positive reaction, of these 2 developed scarlet fever subsequently. Of the remaining cases to the number of 17, 12 did not desquamate.

Tetania Parathyreopriva and Idiopathic Tetany; Functions of Parathyroids.—PATON (*Edinburgh Med. Jour.*, 1924, 31, 541) produces evidence that apparently shows that the increased muscular tone which generally follows removal of the parathyroids indicates that these structures exercise an influence on the tonus of skeletal muscles. The marked increase of muscle tone, and the close similarity of the other symptoms to those produced by removal of the parathyroids which

follows administration of guanidin and its methyl compounds seems to show that they play a part in the maintenance of that tone. The fact that these substances are increased in the blood and urine after parathyroidectomy, and in the urine in idiopathic tetany suggests that metabolism is controlled by the parathyroids and that it is through them that muscular tone is regulated. The immediate action of these substances in one adequate dose is undoubtedly to stimulate the efferent neurons of the spinal cord, and in a moderate dose to increase the excitability of the neuromyons. With repeated doses, they apparently become anchored on these structures to produce a condition of facilitated activity and this probably is their chief mode of action in tetany. That a decrease in the calcium of the blood is not the primary factor in the causation of the symptoms is shown by the effect of bleeding and transfusion of a calcium-free solution, and further by the fact that a decrease of the calcium in the blood may occur without tetany. There is no conclusive evidence to show whether this fall, when it occurs, is a result of the increase in the methyl-guanidin or a concomitant with it. There is no indication that the increase in phosphates plays a direct part in the production of symptoms.

Obesity in Children.—LANGMEAD and CALVERT (*Lancet*, 1924, 2, 1111) have found that the blood-sugar curves in cases of great obesity in children are diverse in their outlines. Their experiments appear to show that pituitary gland substance given by mouth is not inert. As far as carbohydrate metabolism goes, the blood-sugar curve being used as an index, it seems logical to administer that lobe of the pituitary which produces the better effect, on sugar tolerance. Considering the cases generally, the whole gland gives quite good results. The results of the experiments taken collectively might be construed as indicating that a properly blended pluriglandular therapy in cases such as these would be beneficial. Thyroid extract may reduce weight in cases of this kind, but it can hardly be considered as a safe remedy because it does not restore carbohydrate metabolism to normal. Possibly the reduction of the blood sugar may be an useful guide.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Simultaneous Vernes and Wassermann Tests for Syphilis.—BAYLIS, SHEPLAR and MACNEAL (*Arch. Dermat. and Syph.*, 1924, 10, 306), having made an investment in the elaborate equipment required for the performance of the Vernes precipitation reactions, report that the method is a distinct contribution to the exact reading of precipi-

tation tests for syphilis. They conclude that exact mechanical control is possible throughout the procedure by the use of the mixing and dropping apparatus, and that more objective and exact quantitative results are possible than with any other flocculation method. They regard the test as an important check on the Wassermann reaction, but evidently do not accept it as a substitute for the Wassermann procedure which gives more delicate shades of reaction between reagin and antigen.

Incidence of Mixed (Syphilitic and Chancroidal) Infections.—VONDERLEHR (*Arch. Dermat. and Syph.*, 1924, 10, 314) states that 58 per cent of 98 cases of so-called chancroid gave a positive blood Wassermann test on an average of seven and a half months after the development of the venereal sore. Typical chancres are 1.25 times more prevalent than the non-syphilitic venereal sores. Mixed infections are 1.38 times more prevalent, and venereal sores that are syphilitic occur 2.63 times more frequently than the uncomplicated chancroid. Mixed infections constitute 38 per cent of all venereal sores, and their recognition by careful study at first appearance and subsequent Wassermann follow-up deserves emphasis.

An Experimental Study of the Prophylaxis of Syphilis with Arsphenamin, Neoarsphenamin and Sulpharsphenamin.—GREENBAUM and HARKINS (*Arch. Dermat. and Syph.*, 1924, 10, 409) conclude, on the basis of animal experiments, using equivalent adult human doses of arsphenamin, neoarsphenamin and sulpharsphenamin, that a single curative dose equivalent to 0.9 gm. neoarsphenamin will not abort a syphilitic infection if given within three hours after infection. On the other hand three such doses administered on three successive days will abort the infection. It is advised, therefore, that three successive injections of twenty-four-hour intervals be given in the effort to abort a syphilitic infection immediately after inoculation.

Treatment of Ivy Poisoning by Rhus Tincture and Antigen.—WILLIAMS and MACGREGOR (*Arch. Dermat. and Syph.*, 1924, 10, 515) conclude that the method of Strickler (*Jour. Am. Med. Assn.*, 1923, 80, 1588) has greatly improved the therapeutic outlook in severe, fully developed cases of ivy poison. Before the dermatitis becomes marked thorough washing with soap and warm running water and applications of a warm slightly acidulated 1 or 2 per cent solution of potassium permanganate are effective. One year's trial of the Strickler method in the advanced cases has impressed the authors favorably. The antigen should be given in doses of 1 cc from the start, the intervals between injections varying from twenty-four to seventy-two hours. The larger doses were much more effective, and no ill-effects were observed. Rapid improvement usually followed the first dose.

Is Dandruff Seborrheal?—RULISON and HIGHMAN (*Arch. Dermat. and Syph.*, 1924, 10, 429) frankly take issue with the common tendency to regard dandruff as a manifestation of seborrheic dermatitis. They review in some detail the evidence for the actual existence of an entity, pityriasis simplex, which they believe to be due to an infection with the

bottle bacillus of Unna. Upon this infection they believe a staphylococic infection may be superposed. Seborrhea, on the other hand, is, according to the work of Sabouraud, caused by the microbacillus of seborrhea. Seborrhea produces permanent baldness, which it is almost impossible to prevent. Pityriasis produces a gradual thinning of the hair which is easily checked and re-growth may be expected. Seborrhea is not essentially a scaling disease, but pityriasis always is. One may have pityriasis in childhood, and at adolescence develop seborrhea, but in a combination of the two diseases the prognosis as to baldness is that of the more obstinate disease, namely, seborrhea. Infection with the gray staphylococcus (Welch's *Staphylococcus epidermidis-albus*) produces thicker, and more greasy, yellow scales, without the necessary production of seborrhea.

Calcium Content of the Blood in Various Diseases of the Skin, Based on Three Hundred Cases.—SCHWARTZ and LEVIN (*Arch. Dermat. and Syph.*, 1924, 10, 544), on the basis of a considerable series of cases and the review of literature, have concluded that with present methods of determining the calcium content of the blood no great importance can be attached to this item of blood chemistry in dermatology. They observed, however, some improvement from internal administration of parathyroid and calcium lactate in patients with low blood calcium in eczema and furunculosis. They found the calcium content of no importance in urticaria.

Scrofuloderma Gummosa (Tuberculosis Colliquativa).—MICHELSON (*Arch. Dermat. and Syph.*, 1924, 10, 565) calls attention to a type of deep tuberculosis of the skin which begins independently of any underlying tuberculous process in other structures. The process is akin to the scrofulous gumma of the French (tuberculosis colliquativa), the diagnosis of which is always difficult, even if its presence is suspected. It is most likely to be confused with a syphilitic gumma, whose identity can only be recognized by histological examination. The process is more frequently seen in children and especially upon the face and neck. The author isolated tubercle bacilli in his case, but they are usually difficult to find in older lesions. He pertinently emphasizes Volk's warning that when the healing of a furuncle is unduly delayed one should be suspicious of a tuberculous process. A pseudofuruncular onset may mark these cases of tuberculosis colliquativa. The differential diagnosis includes syphilis and sporotrichosis. Tuberculosis is of a livid cyanotic blue, as distinguished from the rusty-red color of a syphilide.

Arsenic Cancer of Occupational Origin.—O'DONOVAN (*Brit. Jour. Dermat. and Syph.*, 1924, 36, 477) reported three cases, all in sheep-dip workers. Sheep-dip contains, mixed with an arsenite of soda, both arsenic sulphide and free arsenious acid. The process of manufacture is very dusty, and the workers usually present arsenical pigmentation. The author gives the face, abdomen, scrotum, buttock, clavicle and lower chest as regions frequently affected. Arsenic cancer has been known since 1820. The constant presence of certain forms of arsenic on the skin in the form of dust can produce carcinoma cutis of the squa-

mous-celled variety. As in tar carcinomata, many years of exposure are needed. The replacement of manual by machine methods of handling, with instruction and periodic medical inspection of workers, does away with the disease. Early operation seems to afford a certain cure.

Fibrosarcoma of the Skin.—DARIER and FERRAND (*Ann. de Dermat. et de Syph.*, 1924, 5, 545) discuss the clinical and histological picture and the treatment of the curious entity known to dermatologists as fibrosarcoma of the abdominal wall. These cases are comparatively rare, and consist in the development of nodular lesions in the skin about the umbilicus, more frequently in males than in females. Small, hard, fibrous nodules fuse to form a plaque, and later multiple tumors develop upon it. The larger lesions become slightly eroded over the surface. The process goes on for years, the lesions gradually breaking down and ulcerating with infection. There is no metastasis to neighboring glands and no involvement of the general health, the condition being purely local in character. Electrolysis and radium therapy are relatively ineffective, the resistance of the neoplasm being remarkable. Surgical extirpation of the fibrous plaque with all its tumors is the only procedure of value, and should be used as soon as the condition is recognized.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Extra-uterine Pregnancy at Full Term.—CATLIN (*Jour. Am. Med. Assn.*, 1924, 82, 107) reports the case of a primipara whose last menstruation began December 12, 1921. Menstruation ceased and pregnancy developed and the patient felt well until January 25, 1922; she then had an attack of pain and faintness which recurred on the following day, and after that at intervals there was pain and some fever. This gradually became so severe that no food could be retained, and the bowels did not move for two weeks. She was then taken to the hospital, anesthetized and a pessary placed in the vagina to support the uterus. The pessary was kept in position for five weeks. After leaving the hospital there was another attack of severe nausea, after which the patient felt considerably better. Fetal movements developed, and the heart sounds were unusually distinct. After a period of unusual movement of the child the fetal movements ceased entirely. On examination the breasts contained a little secretion, the cervix was soft, but with no dilatation, and the body of the uterus could not be made out. There was a bruit on the left side of the abdomen, but no fetal sounds. Apparently the uterus contained a dead fetus, and it was decided to bring on labor by packing the vagina and cervix with

gauze. Four days later the patient was anesthetized and the cervix dilated, when the uterus was found empty. The patient was then removed to a hospital and a roentgen-ray showed the fetus in a sitting posture, with the head at the margin of the ribs and the feet in the left iliac fossa, the back anteriorly, and to the right the shadow of the placenta could be seen apparently attached to the left abdominal wall. On section a thin amniotic sac appeared adherent to the transverse colon and small intestines, and it was impossible to pass the hand around the sac. It was opened at the edge of the placenta, the fluid carefully removed and the child delivered. The fetus was 55 cm. long, weighed 7½ pounds and had been dead several weeks. The effort to remove the placenta was followed by such hemorrhage that it could not be continued. The sac was sewed carefully to the peritoneum, and the wound left open and loosely packed with gauze, which was changed daily. Twenty-seven days after the operation about half of the placenta could be removed without giving the patient pain; a few days later the entire placenta was removed. The wound was kept packed with gauze and several ounces of 1 per cent dichloramin-T were poured into the cavity daily until it became sterile. The abdomen healed perfectly without additional suture. The wide open drainage, it is thought, was responsible for the mother's rapid recovery. The incision was made along the border of the right rectus muscle, and this was thought to be favorable for the complete and rapid union. The blood vessels at the placental site did not close until forty-three days after the death of the child.

Cesarean Section at Seven Months for Premature Detachment of the Placenta in Bifid Uterus.—CARAVEN (*Gynec. et Obst.*, 1924, 9, 184) reports the case of a woman, aged twenty-two years, who had suffered with pain and distress at menstruation. She was about seven months in her first pregnancy. On examination a bifid uterus was found with a pregnancy developing in the left cornu of the uterus. There were symptoms of irritation and pain, and the patient was put at rest with hot applications. She improved and the tumor in the left side increased in size. It gradually assumed the proportions of a seven-months' uterus. The head of the child was uppermost and the body was flexed from left to right. The patient was taken with considerable hemorrhage and premature separation of the placenta was diagnosed. The placenta was above and to the left near the fetal head. At operation the bifid uterus was present, and the pregnancy was as had been diagnosed. The placenta had partially separated. A section of the uterus was at once made, delivering the child, followed by supravaginal hysterectomy with the removal of the appendages. The mother and child made a good recovery.

Hydatid Moles in the Uterus.—BELL (*Jour. Obst. and Gynec. Brit. Emp.*, 1924, 31, 276) describes the case of a woman, aged twenty-four years, a multipara, admitted to the hospital with complete amenorrhea, except for a slight show for one day. The uterus was the size of twelve weeks' pregnancy, the cervix soft and the body of the uterus boggy in consistence. Anterior hysterotomy was performed and a mole easily removed. The patient made an uninterrupted recovery.

On examination the specimen was a mass which comprised vesicles mixed with blood clots; there was a small amniotic cavity without an embryo. On microscopical study the villi had undergone degeneration, and there was considerable blood clot. The specimen was that of a blood mole. The patient stated that her last menstruation had begun and ended eleven months before her admission to the hospital for treatment. The mole had been carried in the uterus then for a considerable time. WILSON (*Ibid*) reports the case of a multipara who had ceased to menstruate, morning sickness had developed and the ninth month after the cessation of menstruation the patient came for examination and the uterus was found to be about four weeks' pregnancy in size, cystic, with a soft cervix. There were no distinctive changes in the breasts or vagina. An examination was made a month later, and there had been no increase in the size of the uterus. The uterus was emptied by passing bougies and giving pituitrin followed by the very slow expulsion of a mole. The patient had a chill following this, but the temperature fell to normal and the patient recovered. On examination there was an amniotic cavity containing a fetus 12 mm. in length, while the remainder of the specimen consisted of vesicles which were degenerated villi.

Pregnancy Complicated by Encephalitis Lethargica. HERD (*Jour. Obst. and Gynec. Brit. Emp.*, 1924, 31, 267) reports the case of a primipara, aged twenty-four years, with headache and edema of the ankles in the thirty-sixth week. After severe frontal headache the patient had what was said to be a convulsion, and was removed to the hospital as a case of eclampsia. On admission she was restless, her color was good, station was normal and blood-pressure was 130. The gestation was normal at the thirty-sixth week. The cervix admitted two fingers and the membranes could be felt. The urine taken by catheter was highly albuminous; within six hours after admission the patient had six fits without cyanosis and regained consciousness within five minutes. Then there were convulsions with marked cyanosis similar to those of eclampsia. Consciousness was gradually regained, and labor developed with spontaneous birth of a living male child. The placenta was delivered spontaneously and showed no abnormality. For the first five days after delivery the patient remained partially comatose, restless, with rhythmic contraction of the muscles of the lower jaw, temperature ranging from 99.6° to 102° F. Albumin was always present in the urine, but the blood urea was not high. Involution proceeded normally. The patient had been treated by lavage of the colon, blood-transfusions with citrated blood and two injections of morphin ($\frac{1}{8}$ gr.) were given on the first day. The patient was transferred to a general hospital, where she died on the twentieth day after delivery. At autopsy a careful search was made for evidences of toxemia but none were found; the condition was typically encephalitis lethargica. His second case was a primipara who in the thirty-fifth week became sleepless and neuralgic, attributed to fright. There was nothing to suggest toxemia. On admission to the hospital the patient was excited, restless, rational and with a normal pulse and temperature. There were continuous movements of the muscles of the head, face and limbs. The eyes were normal and so were the reflexes. The urine contained con-

siderable albumin. The thyroid gland was not enlarged, and the patient was very constipated. At first she was thought to have chorea, but treatment addressed to this condition was without result, and the case was then recognized as one of encephalitis lethargica. On the fourth day the patient gave birth to a still-born, non-macerated female child, and during labor and afterward was unconscious for some time. The temperature rose from 100° to 102° F. During the next four days she was semiconscious, restless with delusions and subsequently her condition improved, but complete recovery did not occur and is not expected. Postmortem examination of the child revealed nothing of significance.

A Study of the Syphilitic Placenta.—MÖNCKEBERG and AVILÈS (*Gynec. et Obst.*, 1924, 9, 419) have made a histological and pathological study of the syphilitic placenta, and illustrate their findings. The predominant lesion is that of hematosiis which, in proportion to its severity, affects the nutrition of the fetus. The different lesions found were infarcts, endarteritis, necrosis of the villi, thrombosis, hemorrhage, the diminution in the capacity of the blood channels of the placenta—these conditions may result in the death of the embryo. The writers bring up the question of the presence of the treponema pallidum in the syphilitic placenta. They could not successfully isolate this germ in the placenta and question whether this was due to faulty technique. In 30 per cent of the fetuses studied in these cases the treponema was found in the liver, so that they believed the failure to find it was not through an error in technique.

The Live Method of Obstetric Teaching.—GREEN and ARMYTAGE (*Jour. Obst. and Gynec. Brit. Emp.*, 1924, 31, 218) state that the roentgen-ray study of labor made by Warnekros, and Hollands' *Researches on Intracranial Strains* has thrown new light on the mechanism of labor and require new methods of demonstration and teaching. To make teaching more interesting the writers take twenty students at a time for six weeks: each morning one hour is devoted to clinical gynecology and one hour to clinical obstetrics. They use for demonstration an especially made large female dummy, lined with a clean warm turkish towel, and in this is placed, shortly after it has been nursed, a recently born baby, up to ten days old. One by one the different presentations are taken up, the mechanism of labor is demonstrated and complications and treatment reviewed. The movements of the live child, clothed in one thickness of garment only, impress the student. The cord is illustrated by red tape sewed to the clothing, and with the dummy turned on its left side the reason for flexion and the mechanism of the perineum can be observed. By placing one or more small flat hand towels under the lining towel, between the sacral promontory and the baby's head, a moderate contraction of the pelvic brim of the model is made, and the study can be carried out of the relation of the head to the pelvic brim, and the various tests of labor. The writers make every demonstration a clinical lecture, using living material on all occasions. Classes should be held in a warm room near the lying-in ward. Each class should not be greater than twenty. The assistance of nurses is always needed. The baby should be a small and

healthy one, and if carefully handled no harm can be done. In inducing labor when a bougie could not be obtained, the writers have used rubber tubing, into which they inserted a thin piece of bamboo or flexible stick; a piece of silk was tied tightly around the tubing just above the end of the stick. To demonstrate the method with the live baby, a conical bag of clean canvas or linen was used which was fitted loosely over the child's head, with the apex representing the cervix. This apex of the bag may be grasped by forceps, opened with scissors to represent the open cervix and bougie can then be introduced as a demonstration. By using rubber sheeting the pelvic floor can be represented and its mechanism and lacerations can be taught. The placenta can be represented by a sponge and other similar methods are available. The writers believe that when inexpensive materials are employed, the constant presence of the instructor and the use of living material will make obstetric teaching far more efficient. He does not believe the use of a still-born fetus is efficient. He adds two illustrations, with small tracings of the pelvic floor.

Etiology of Certain Congenital Defects.—BAGG (*Am. Jour. Obst. and Gynec.*, 1924, 8, 131) contributes an illustrated paper upon this subject, presented before the New York Obstetrical Society. His work consisted of experiments upon animals to determine the effect of the roentgen-ray and other sources of possible malformation. He finds that structural defects arise from arrested development with blood vascular disturbances. In some cases this is poor blood affecting the vascular endothelium or other conditions in the vessels. The local area of such extravasation occurring at a critical period in the development of an organ may interfere with processes of development and thus lead to structural defects. In experimental work the eyes of animals are often affected because the bloodvessels of the head readily give away and permit extravasation of blood. Club feet and syndactylism are the result of these changes in the extremities. Entire organs are sometimes affected, such as the kidneys, and their development may be partially or wholly suppressed. In newborn children many such lesions in the head can be traced to birth injury by instruments, pelvic pressure or partial asphyxia and increased blood-pressure during labor. Similar hemorrhages, however, have been found in children examined in the uterus during Cesarean section. In these cases birth pressure plays no part. Congenital nevi indicate that such blood disturbances occur in the prenatal period. Club feet are often ascribed to the faulty position of the child in the uterus or to paralysis and malformation of the affected limb. No light is thrown on this subject by the study of the development of abnormal structure. Cases where the eye is poorly developed or is entirely lacking may be traced to these blood vascular disturbances.

Anesthesia in Obstetrics.—BOYLE and HEWER (*Jour. Obst. and Gynec. Brit. Emp.*, 1924, 31, 264) have summarized their experience at St. Bartholomew's Hospital. For analgesia during normal labor the patient is allowed to give herself nitrous oxide as she feels the pains approaching. For the application of forceps pure gas-oxygen they believe to be an ideal method. For Cesarean section, in addition

to gas-oxygen, some ether is necessary, and if the percentage of oxygen be increased just before delivery the baby will be bright red in color and will cry instantly. The suturing of the uterus and of the abdominal wall can generally be done under gas-oxygen alone, as the muscles have been stretched during pregnancy and absolute relaxation is unnecessary. This method of anesthesia also suffices for induction of labor and other vaginal operations. A highly nervous patient may receive morphin and scopolamin before taking the gas-oxygen and ether or ethanesal. As regards spinal anesthesia, they do not consider it safe in comparison with general anesthesia. The mortality of this method they believe to be about 1 in 400. They believe that the endotracheal method of anesthesia will be superior to others for major pelvic surgery. They advocate the combination of gas-oxygen, ethanesal and chloroform. The patient is first anesthetized fairly deeply by inhalation, and under the guidance of a laryngoscope a tracheal catheter is passed and gas-oxygen and chloroform are given down the catheter until the patient ceases to cough, and the chloroform is turned off and ethanesal substituted. Respiration is extremely shallow, and can be stopped if desired and the color of the patient is always good. This results in an absolutely relaxed abdominal wall and without protrusion of the intestines and without congestion of the lungs. This must be given with proper apparatus and by an expert to be successful.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Chemical Hysterectomy.—Chemical hysterectomy is presented by BABCOCK (*Amer. Jour. Obst. and Gynec.*, 1924, 7, 693) as an additional measure for the removal of the essential parts of the uterus, but it is to be used with care and good judgment. It has a somewhat limited field and will not eliminate the use of radium in gynecology or the scalpel for hysterectomy. Obviously more dangerous than radium and, therefore, not even a competitor against the simpler forms of uterine bleeding, it has the advantage of permanency of action and the elimination of any associated uterine infection. It is probably more certain than simple ligation of the Fallopian tubes or the use of the roentgen-ray or radium in producing sterility and some surgeons may welcome this method as a means of escaping from an occasional very difficult or dangerous hysterectomy. In performing this operation the patient is prepared and placed in position as for a uterine dilatation. Local, nitrous oxide or narcotic anesthesia may be used. The cervix and inter-

nal os are dilated sufficiently for the introduction of a uterine packer. The cavity of the uterus is explored and scrapings or discharge is removed for laboratory study. A uterine packer, preferably with an obturator is introduced well through the internal os and the cavity of the cervix and uterus thoroughly packed with a narrow gauze tape impregnated with a saturated solution of chlorid of zinc. During this procedure the vagina is protected with a strip of gauze impregnated with dry sodium bicarbonate that extends from behind the cervix out under the weighted vaginal speculum. The vagina is now so packed with other strips of soda-impregnated gauze that the cervix and the caustic tape issuing from the cervix, are completely surrounded. The packing, including the caustic tape, is withdrawn in seventy-two hours or less, dependent on the amount of gauze used and the thickness of the uterine walls. The uterine slough will usually come away about the end of a week and it is wise to keep the patient in bed one week and under supervision for nine days. Rarely is a secondary packing required. Marked secondary oozing is not usual, but should it occur, the patient should be put in the knee-chest position, a speculum inserted and the vagina carefully packed with gauze after dusting in 5 or 10 gr. of alum. If the slough has not been expelled by the ninth day, it should be removed by forceps or the finger, provided it is no longer attached to the uterine wall. Babcock gives specific instructions concerning the preparation of both the caustic tape and the alkaline gauze and also the method of computing the length of time that the tape should be left in place in various types of cases.

Etiology of Cancer.—For many years WILLY MEYER (*Jour. Cancer Research* 1924, 8, 45) has been deeply interested in the subject of cancer and its causation and in his Presidential address before the American Association for Cancer Research he summed up his present belief concerning the etiological factors in cancer. He reminds us that by general agreement of competent investigators the observation is throughout accepted as a fact that spontaneous cancer cells descend from normal cells of the tissue in which the cancer arises. To the process of transformation of the cells from one state to the other, parasites, like numerous other non-specific factors, such as mechanical, thermal, actinic, chemical, endocrine, hereditary, stand in the relation of the match to the heat radiating from the fire which it has kindled, viz. inciting but incidental. Current experimental production of primary cancer by various non-specific means makes the search for the specific cancer agent appear as no longer advised, and seems to prove that irritation is ordinarily the starting point of developments tending in the direction of cancer. As nearly as anything can be certain in medicine, there is no cancer contagion or specific infection, since observations seem to prove that cancer is in every instance an individual experience. More than one individual may receive a non-specific inciting factor from the same source, and then independently, by reason of the same, may or may not develop cancer. Around a source disseminating directly, or indirectly through intermediate hosts, one or more non-specific inciting factors, "cancer houses," "cancer districts," "cancer towns" may grow up and in order to reduce cancer incidence such common sources should be sought out and abated. One such source seems

to be the rat. Systematic rat extermination, already suggested for economic and hygienic reasons, appears advisable from the point of view of reducing the number of cancer-inciting factors. From the same point of view prophylactic anthelmintic treatment at frequent regular intervals throughout life, applied as broadly as vaccination against smallpox, might possibly work a reduction of cancer incidence, according to Meyer. Such a proceeding would be of still greater value if in addition means could be found to reach and render harmless the larvæ in the various organs.

The Time for Operation in Ectopic Gestation.—There always has been and probably always will be a controversy as to whether ruptured ectopic pregnancy demands an immediate operation or should be watched temporarily until the period of shock is passed. All will agree that it is most dangerous to operate while the patient is in shock, but on the other hand, in some cases of the tragic type, the patients never react and die if untreated. Some interesting studies on the systolic blood-pressures in these cases have been made by WELTON (*Amer. Jour. Obst. and Gyn.*, 1924, 7, 158) who concludes that nothing is gained by operating while a patient is in shock for he states that if the patient does not die at the time of her initial collapse, it denotes she will respond, to a certain degree, to measures in treatment. He believes that all ectopic pregnancy cases should be given a trial to demonstrate what they can do by way of a recovery, which will be well shown by the systolic blood-pressure readings. In all unruptured ectopics, surgery is the rule. If the pressure continues to fall in spite of treatment, surgery is imperative. Similarly, in a pressure that reacts to, at the maximum, 115 mm., operation is indicated, because if the pressure is permitted to return to normal, the sealing clot may be disturbed and renewed hemorrhage and shock occur. In the moribund type of case, with an initial pressure of 50 or lower, the rise is never back to normal limits. It is important to remember that a pressure that rises and then remains stationary calls for surgery: The length of time to wait while a pressure remains stationary depends upon the type of case, and is governed by the experience of the operator. Any pressure that rises and then begins to fall calls for immediate surgery. On the whole, the systolic blood-pressure is a very good index of the patient's condition.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

ASSISTANT PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

A Study of Hypersensitiveness to Derivatives of Hemolytic and Non-hemolytic Streptococci.—MACKENZIE and HANGER (*Proc. Soc.*

Exper. Biol. and Med., 1924, 21, 442) tested a large number of patients with a variety of conditions, using filtrates and extracts of hemolytic and non-hemolytic streptococci obtained from the interior of tonsils immediately after tonsillectomy. The intracutaneous injection of 0.01 to 0.04 cc of filtrates of young broth cultures produced in nearly all adults positive reactions, which developed after a latent period of eight to twelve hours. The intensity of the reaction varied from a central red, slightly tender elevation surrounded by slight swelling and erythema, 1.5 to 2.5 cm. in diameter, to stronger reactions consisting of a central pustule which always proved to be sterile on culture. The pustule was surrounded by a red, hot, indurated zone with an erythematous halo, measuring as much as 10 to 12 cm. in diameter. The full intensity of the reaction was attained after twenty-four to forty-eight hours, fading in two to ten days and leaving a pigmented spot with a fine desquamation in some cases. Very young children did not react to the substance. The non-hemolytic streptococci obtained from routine throat cultures in the absence of acute infection were much less capable of producing active filtrates than non-hemolytic streptococci obtained from excised tonsils. Certain non-hemolytic streptococci quickly lost the capacity to produce the active substance when cultivated outside the body. The active substance present in the twenty-four-hour filtrates withstood boiling and did not rapidly deteriorate when kept at ice-box temperature. Some individuals reacted more strongly to filtrates, others to constituents of the bacterial cell.

Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Cardiac Disease of Rheumatic Origin.—"The question as to whether the still unknown virus of acute rheumatic fever may localize in the aorta has not been satisfactorily answered." Consequently, PAPPENHEIMER and VON GLAHN (*Jour. Med. Research*, 1924, 44, 489) conducted a comparative histological study of the aortæ in a series of 76 rheumatic cases, and in 77 non-rheumatic cases, dying from a variety of diseases, as well as an equally large series of syphilitic aortitis cases. In the selection of cases for the rheumatic group the authors based the diagnosis upon the clinical history of one or repeated attacks of rheumatic fever, or of chorea, or of repeated attacks of tonsillitis; upon the finding of typical rheumatic lesions at autopsy, namely, verrucose endocarditis, showing the characteristic structure and absence of bacteria in sections; upon Aschoff bodies in the myocardium associated in the recurrent cases with the elliptical perivascular areas of fibrosis; upon fibrinous pericarditis or pericardial adhesions, and chronic mitral disease, not arteriosclerotic. The sections for microscopical examination were stained with hematoxylin-eosin, with Weigert's elastic tissue stain, followed by hematoxylin and van Gieson's picrofuchsin and with the Una-Pappenheim methyl-green-pyronin method. The most distinctive lesions encountered in the rheumatic group were the dense and often acellular scars in the vicinity of the nutrient vessels, and the Aschoff cells or nodules in the adventitia. In comparing the lesions with those found in syphilis, the authors called attention to the fact that in syphilis there is a much greater lymphoid and plasma cell reaction in both media and adventitia. The rheumatic scars

remained confined to the vicinity of normal penetrating vessels, whereas the syphilitic granulation tissue was attended by the formation of new capillaries and the resultant scars were far more extensive and led to a far greater destruction of elastic and muscular fibers. The authors concluded that "further study is necessary to determine the distribution of the lesions in the aorta, the possible occurrence of similar changes in peripheral vessels and their clinical significance."

Inoculation and Implantation Experiments in Monkeys with Glands from Cases of Hodgkin's Disease.—The experimental results obtained in Hodgkin's disease can be placed in one or other of the three following categories: (1) The production of a tuberculous lesion in experimental animals by the injection of Hodgkin gland emulsions (Cignozzi, 1906; Schaeffer, 1914); (2) the reproduction of the histological changes of the disease as seen in man by the injection of cultures of a diphtheroid bacillus recovered from the lymph glands in cases of Hodgkin's disease (Bunting and Yates, 1913, 1914); (3) negative findings (Longcope, 1908; Torrey, 1916; Cunningham and McAlpin, 1923). These various results are in keeping with the different views as to the etiology of Hodgkin's disease, arrived at by various observers on other grounds, namely, that it is: (1) An atypical form of tuberculosis; (2) a specific infection by a diphtheroid bacillus; (3) a granuloma of unknown etiology; (4) a neoplastic disease. STEWART and DOBSON (*Brit. Jour. Exper. Path.*, 1924, 5, 65) inoculated 3 rhesus monkeys with lymph glands from a case which showed a well-marked eosinophilia in the glands, and 1 bonnet monkey with the glandular material from a case which did not show eosinophilic cells, but which exhibited microscopically, typical, active cellular Hodgkin's disease. In each experiment laparotomy was performed, and some small chips of a Hodgkin gland just excised from the patient were implanted into some of the mesenteric lymph glands or into the spleen, or both. One rhesus monkey, after four and a half months, showed an unusual degree of simple hyperplasia of the lymphoid follicles and of the Malpighian bodies of the spleen, especially of the germ centers in each instance, together with a peculiar giant-cell reaction, probably of foreign-body type, around the implanted material. The remaining experiments yielded completely negative results, the bonnet monkey being under observation for three years and 1 *Macacus rhesus* for two years before they were sacrificed for examination. The authors conclude by saying that "These experiments afford further proof that whether or not Hodgkin's disease is an infective granuloma, it is at least not due to a virus capable of reproducing the disease in monkeys."

The Prevention and Cure of Rickets by Means of Bile.—Since it has become well established that cod-liver oil prevents and cures rickets, KAPSINOW and JACKSON (*Proc. Soc. Exper. Biol. and Med.*, 1924, 21, 472) conducted a series of experiments on thirty-two-day-old rats to ascertain whether products of mammalian liver, in particular bile, might not exert a similar action. The rats were divided into

two groups. To one group freshly obtained gall-bladder bile from the pig was added to a rickets-producing diet which was given for a period of thirty-five days. In the other group rickets was produced by giving the diet and then bile was added to the diet and given to the animals for a period of fifteen days. It was found that 7 cc of pig bile per day prevented the development of rickets in the rats of the first group, while 3 cc of pig bile per day did not completely prevent the development of rickets and 1 cc exerted a well-marked inhibitory action. In the second group 7 cc of pig bile per day completely cured rickets when fed for a period of fifteen days; 5 cc and 2.5 cc of bile per day did not completely cure rickets, although 5 cc exerted a manifestly greater curative action than 2.5 cc. The control rats all showed rickets.

A Fatal Infection with an Organism of the Proteus Group.—As cases of fatal infection with organisms of the proteus group are rare, WARREN and LAMB (*Jour. Med. Research*, 1924, 44, 375) report an instance which occurred in a man, aged thirty-one years, who was suffering from myelogenous leukemia, tuberculosis and a severe Vincent's angina. The proteus-like organism was isolated from two antemortem blood cultures and from postmortem cultures of the heart's blood, pericardial sac, liver and spleen. According to morphology, mobility, proteolytic activity and fermentation reactions, the organism could be identified as a member of the proteus group, although it did not correspond to any previously described organism. It was pathogenic for laboratory animals, causing septicemia and necrosis of liver, heart muscle and adrenals. The filtrate of young broth cultures were toxic and had similar pathological effects on the tissues to those produced by the organisms.

Variations in the Number of Blood Plates Associated with a Common Cold.—It has been shown that the disappearance of microorganisms from the blood stream into which they have been introduced is preceded by their agglutination and that this agglutination is brought about by the blood plates. From these and other findings it appears that the blood plates are concerned in the resistance to bacterial infection and a determination of plates to the site of action would infer at least a temporary fall in their number in the circulating blood whence they are drawn. BANNERMAN (*Brit. Jour. Exper. Path.*, 1924, 5, 16) had an opportunity to observe the fluctuation in the daily blood-plate counts of an individual with an apparently arrested pulmonary tuberculosis, who developed an acute nasopharyngeal "cold." The average plate count of this person in his normal condition lay in the region of 340,000 per c.mm. During the "cold" the number fell to about 240,000 per c.mm. until the terminal stages of the "cold," when a rise above the normal average occurred and was then followed by a resumption of the normal level.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Malta Fever: Cattle Suggested as a Possible Source of Infection.—EVANS (*Pub. Health Rep.*, 1924, 39, 501) summarizes her work as follows: Five hundred human serums from patients suffering with a variety of diseases were tested for agglutinins specific to *B. melitensis*. Fifty-nine, or 11.8 per cent, gave a definitely positive reaction in dilutions of 1 to 5 or higher. One serum had a titer of 1 to 320, which would lead to an unquestioned diagnosis of Malta fever in regions where the disease is endemic. The patient was unaware of any possibility of having contracted an infection from goats. He was in the habit of drinking raw cow's milk. Absorption tests with the serum showed that this patient was infected with the *abortus* (bovine) variety of *B. melitensis*. The titers of the remaining 58 serums which gave positive reactions varied from 1 to 5 to 1 to 40. The suggested explanation for these positive reactions is that the agglutinins were produced as a specific response to *B. melitensis* ingested in cow's milk, although such an infection may not necessarily have caused a notable illness.

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The Prevalence and Trend of Drug Addiction in the United States and Factors Influencing It.—KOLB and DUMÉZ (*Pub. Health Rep.*, 1924, 39, 1179) give the following summary and conclusions: The evidence seems to show that a maximum estimate for the number of addicts in the United States at the present time would be 150,000. The estimates based on actual counts and on the available supplies of narcotics, together with the conditions reported by the physicians interviewed, point to about 110,000, which number is believed to be nearly correct. The number of addicts has decreased steadily since 1900. Before this decrease set in there may have been 264,000 addicts in this country. The greater number of addicts in prison at present as compared with former years is due to the rigid enforcement of recently enacted laws and not to an increase in the prevalence of addiction. The average daily addiction dose of the opiates in terms of morphin sulphate or heroin hydrochloride is not less than 6 gr. The dose of cocaine hydrochloride is practically the same. The quantities of narcotics imported by this country at the present time are believed to be only slightly in excess of the amounts required to supply medicinal needs. While physicians have been credited with being responsible for the creation of many addicts in the past, it is concluded as a result

of our studies and observations that but few cases of recent addiction can be so attributed. Before the enactment of restrictive laws in this country there was much opium smoking and addiction to gum opium and laudanum. Today addicts use the alkaloids or their derivatives almost exclusively. Cocain hydrochloride was used alone by a large number of addicts prior to 1915, but is now used only in conjunction with the opiates except in a few cases. The proportion of the delinquent type of addict is gradually increasing. This is apparently not due to an increase in the number of this type, but to a gradual elimination of normal types. From the trend which narcotic addiction in this country has taken in recent years as a result of the attention given the problem by the medical profession and law-enforcement officers, it is believed that we may confidently look forward to the time, not many years distant, when the few remaining addicts will be persons taking opium because of an incurable disease and addicts of the psychopathic delinquent type, who spend a good part of their lives in prisons.

Epidemiological Principles Affecting the Distribution of Malaria in Southern United States.—MAXCY (*Pub. Health Rep.*, 1924, 39, 1113) enumerates the following factors which determine the distribution of malaria: (1) Anopheline mosquitoes which feed upon man must be propagating in sufficient numbers within flight range (about 1 mile) of human habitation; (2) human beings with the sexual forms (gametocytes) of the malaria parasite in their peripheral blood must be accessible to and bitten by these mosquitoes; (3) temperature must favor completion of the life cycle of the parasite in the mosquito; (4) if the level of prevalence is to be maintained, infectible human beings must be accessible to and bitten by infected mosquitoes so that at least one new infection occurs for each old one that recovers. Given the conditions which we at present know to be favorable, a careful survey for enlarged spleens or parasites may (or may not) show a malaria problem to be present. On the other hand there are large areas where conditions exist which are obviously unfavorable to the transmission of malaria, that is where the population is composed of enlightened, well-to-do white families living in well-screened houses in prosperous sections on cleared, cultivated, and thoroughly drained farm land and in towns with the best sort of medical attention. To persons living under these conditions malaria is practically an unknown disease. It follows, then, that malaria is not an ubiquitous disease in southern United States, as is, for instance, such a disease as measles. It exists where certain more or less well-known requirements as to the mosquito host and the human host are realized. *Malaria is characteristically a focally distributed disease.*

Foci are classified as follows: (1) Endemic—where conditions are favorable for the transmission of malaria year after year. (2) Epidemic—universal prevalence, usually due to new conditions or circumstances. It should be emphasized that there may be a considerable element of chance in epidemic outbreaks of this type. It is a fortuitous circumstance that at the particular time when Anopheles are more abundant than usual, a malaria patient with many gametocytes in the peripheral circulation is housed in a location most exposed to the bites of these mosquitoes; and that subsequently, although perhaps only one

of these mosquitoes survives to become infective, this mosquito happens to reach a room or a tent in which many persons are sleeping and takes an infecting blood meal on several of them, thus precipitating an outbreak. There are many places in this chain of events where the sequence may be and probably is interrupted much more frequently than it is successfully completed. (3) Potential—where one or another form is usually absent but where all may occasionally be present, resulting in an outbreak. For instance, all the factors may be present at a given time except a carrier accessible to the bites of *Anopheles*; and, if one happens along at this particular time, transmission occurs. Or, all the factors may be present except a sufficient number of *Anopheles*, the creation of a small pool of water by the filling up of an old drainage ditch or culvert, or by the building of a roadway, having furnished the missing link. In a prison outbreak, the production of a small number of *A. quadrimaculatus* in close proximity to a crowded, unscreened camp, constituted a potential focus. It became an epidemic focus when a human carrier appeared upon the scene.

Maxey's summary is as follows: The factors favorable for the transmission of malaria in southern United States are now fairly well known. The disease is not ubiquitous, but exists in those localities where certain rather highly specialized conditions are realized. Where these conditions are present continuously year after year, the focus is endemic, where brought into existence suddenly by some unusual circumstances, the focus is epidemic; where they may be realized at any time, though one or another factor is usually absent, the focus is potential. Numerical expression of the amount of malaria in a given rural area is not so necessary to the practical health administrator as is a clear understanding of the distribution of the disease. Sufficient field study should be made to establish the localities in which the disease is indigenous and the relative importance of different foci to the surrounding country from an epidemiological point of view. Efforts to control the disease must be directed ultimately toward the endemic centers. The measure of effective control is the demonstration that the amount of malaria transmission taking place is no longer considerable so far as community measures are concerned.

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All communications should be addressed to—

DR. EDWARD B. KRUMBHAAR, The Laboratories, Philadelphia General Hospital, Thirty-fourth Street below Pine.

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ORIGINAL ARTICLES.

PAIN PHENOMENA OF THE FACE, THEIR ORIGIN AND TREATMENT WITH SPECIAL REFERENCE TO TRIGEMINAL NEURALGIA.

BY CHARLES H. FRAZIER, M.D.,
PHILADELPHIA.

(Read before the Section on Oral Surgery of the First District Dental Society of New York, October 22, 1924.)

THE consideration of sensory disturbances in the region of the face, more particularly pain phenomena, at once opens a field in which there is abundant opportunity for discussion—a discussion which if followed beyond a very superficial study, takes us into the realm of comparative as well as human anatomy and physiology. While attention will be focused chiefly on *major* trigeminal neuralgia we cannot disregard other forms of painful affections, which in their persistence and in their severity as measured by the patient, are equally distressing and command our attention.

In the region of the face the predominant nerve of sensation is the trigeminal, but it must not be forgotten that in the facial nerve also there are sensory fibers and that at least some parts of the sympathetic system, as in the visceral distribution, perform a sensory function.

Primarily the entire function of the nervous system was represented by sensory and motor structures whose nuclei were distributed throughout the spinal axis, but as the brain became differentiated certain groups of spinal cells, both motor and sensory, became the nuclei of the cranial nerves.

The trigeminal and facial nerves operate physiologically in the same territory, and if studied phylogenetically, we find in the lower

forms of animal life a close alliance between them. Thus in the aquatic lower vertebrates the facial receives a large reinforcement of sensory fibers, part of a septum of cutaneous end-organs. Some of these, as in fishes, serve for the perception of pressure sense. Furthermore in the primitive forms (amphibian group) the root fibers of the facial nerve are often so intermingled with those of the trigeminus that it is difficult or impossible to differentiate, in their course from their nuclei to the points of emergence from the pons, the fibers of these two nerves one from the other. Not only therefore are their nuclei in close proximity, but their fibers intermingle.

In the consideration of pain phenomena of the face, should one overlook the sympathetic system? For some reason or other, throughout the trigeminal tract nature made abundant provision for sympathetic control or association; for example there are the sympathetic fibers from the internal carotid plexus to the Gasserian ganglion, there is the ciliary ganglion of the ophthalmic division, the sphenopalatine of the maxillary division and the otic and submaxillary ganglia. These rich sympathetic connections may not be without their significance. Operations upon the cervical sympathetic ganglia have been practised many years for the purpose of relieving pain as in trigeminal neuralgia and migraine. I will not discuss these now, but would like to call your attention to the fact that when one stimulates electrically the cervical sympathetic ganglion or the periarterial sympathetic plexus of the common carotid artery, as I have a number of times in operations on the neck under local anesthesia, the patient frequently complains of pain within the zone of the trigeminal distribution.

The major theme of our discussion has to do specifically with major trigeminal neuralgia, and while in most instances this disease is readily recognized by the mere recital of the patient's history, there are other forms of neuralgia with which it may sometimes be confused. The term neuralgia obviously implies pain and yet there are of course many degrees of pain. A moderate degree of surface pressure might lead to discomfort but if continued with increasing force it may readily elicit pain, but the precise point at which this transition between discomfort and pain takes place would be difficult to determine, and can be interpreted only by the patient. And so with all neuralgias we are dependent entirely upon the patient's description and upon his estimation in his own terms, of the degree of pain. As pain is a subjective phenomenon we have no means other than the patient's statement as to the intensity of his suffering. The possibility therefore, of being misled by exaggeration either intentionally or unintentionally on the part of the patient, must not be forgotten, and we must be on our guard especially in neurotic subjects and drug addicts lest we be persuaded to resort to such radical procedures as the circumstances may not justify.

The significant features of these neuralgias obviously is the almost purely subjective character of the symptoms. There are, with some exceptions, no objective signs upon which a differential diagnosis may be established. One must listen patiently to the story and the description as told by the one afflicted and have the account repeated often in order that the clinical picture may be clear and not confused. Sometimes it is difficult, if not impossible, from the patient's own words to secure a picture clear enough to satisfy the examiners. The more confused and indefinite the picture, the more the pain expression varies in character and location in the individual case the surer one can be that the neuralgia belongs not to any one of the more definite types, such as tic douloureux or herpetic neuralgia, but to that miscellaneous medley of pains and discomforts which baffle us oftentimes both as to diagnosis and treatment.

Just as there are many degrees, so there are many kinds of pain. In our analysis of 1025 cases of neuralgia that have been observed in the Neurosurgical Clinic of the University of Pennsylvania Hospital, without any preconceived notion as to classification, we found at least three different types of sensory disturbance: (1) Pain sensation, using the term in its descriptive sense as opposed to other forms of sensation such as tactile, thermal or pressure; (2) pressure sensation, and (3) thermal sensation. Presumably it is reasonable to postulate that in a lesion of any sensory nerve there may be disassociation of sensation, so that it is not surprising to find in a lesion of the trigeminus these varying expressions of disturbed sensation, classified as they are under pressure, thermal and pain. For example, under disturbance of thermal sensation we might include, "burning," "smarting," "stinging" pains, or, to use a not infrequent descriptive phrase, "the feeling of a hot iron." Under disturbance of pressure sensation could be included "boring" "grinding" "squeezing" or "drawing" pain; and under disturbance of pain sensation, using the word in the technical sense again as of that of a cutting instrument, "stabbing," "cutting," "sharp," "pricking," and "piercing."

But to what end is this sketchy review of the problems relating to the source and to the character of painful phenomena in the face? It may serve a useful purpose if only by bringing into relief the variability of these phenomena, the obscurity of their origin and the need for continued and painstaking observation in the hope that they will bring to light certain aspects of these painful nerve lesions that are now obscure.

From this more or less theoretical discussion, we turn now to a systematic review of the various forms of neuralgia to be considered in a differential diagnosis.

1. There is in the first place the neuralgia that is a sequel to infection as of the teeth or sinuses, a neuralgia due in all probability to a peripheral neuritis, to an inclusion of the peripheral or terminal

filaments of the trigeminal nerve in the inflammatory process. I need scarcely more than refer to it, as you are familiar with this commonplace ailment. The pain, originating with infection, is more or less constant, often throbbing in character and subsides with the subsidence of the inflammatory process. Above all, be it said that the pain is not paroxysmal, coming and going with intervals of complete freedom. At no time should there be any reason for confusing this form of neuralgia with the so-called *tic douloureux*.

2. Then we have the postherpetic neuralgias. There has been an attack of herpes zoster or "shingles" in one or the other branch of the trigeminus, more frequently the supraorbital, and the pain is of greatest intensity during the "zoster" attack. Again the pain is not paroxysmal but more or less constant with perhaps exacerbations. One of the conspicuous and distinguishing features of postherpetic neuralgias is hyperesthesia of the skin.

3. There are the neuralgias, relatively infrequent to be sure, that accompany tumors of the Gasserian ganglion and of all the facial neuralgias, these are most likely to be confused with the major trigeminal form. But there are certain distinctive features which, if recognized at once, serve as signs of differentiation. I refer particularly to certain *objective* disturbances of the skin and especially to hypesthesia, observed first in the cornea.

4. There are certain painful phenomena of the face (neuralgia is not an appropriate or descriptive term, although usually used in this connection), which are associated with the hemicranias or migraine. The vasomotor disturbances, one sees in the truly migrainous subject, as expressed by the sudden pallor or sudden flushing of the face, by the pupillary dilatation, by the salivation, are distinguishing features.

5. Second in frequency is that group of miscellaneous neuralgias which, for a better understanding either as regards to origin or treatment, we call "atypical," very much as we applied at one time the term "idiopathie" to certain forms of epilepsy, the origin of which was obscure. These "atypical" neuralgias are not due to infection, as of the sinuses though many a sinus has been drained in the vain hope of relief. As compared with other forms of neuralgia and particularly with *tic douloureux*, there are many distinguishing features. The pain is not referred to the periphery, as to the lips, chin, alae of the nose, is not related to anatomic zones, as to one or the other supplied by branches of the trigeminal nerve, it may and often does extend beyond the trigeminal territory, as to the neck, submaxillary or retromastoid region. Pain, referred chiefly to the malar region, the orbit and temple, usually is described as pulling or drawing, as boring or as an ache. The sense of pressure or tension often seems predominant. It is constant, not paroxysmal, worse by night rather than by day and may be relieved by opiates.

Carry this picture in your mind and at once you will differentiate it from the next and last group.

6. Major trigeminal neuralgia, tic douloureux, epileptiform neuralgia, la grande neuralgie, surgical neuralgia, trismus dolorificus, an array of descriptive terms giving in themselves a composite picture of the kind of neuralgia they designate. I need not enlarge upon the clinical characteristics of a disease, described as long ago as 1776 quite as accurately as though the description were written today. Suffice it to say that a diagnosis of major trigeminal neuralgia should not be considered justifiable first, when there is an associated area of hypesthesia or anesthesia in the trigeminal zone; second, when the pain is continuous and not paroxysmal; third, when in the early stages there are not intervals of complete freedom; fourth, when the pain does not correspond to the anatomic zones, and last when the pain is not referred primarily to the terminal areas of nerve distribution.

Did time allow I should like to discuss the etiology of these several forms of neuralgia. In some forms the cause is quite obvious and in some the discussion would take us far afield in the realm of speculation. As major trigeminal neuralgia is of particular interest to the oral surgeon, I will say a word as to its etiology with reference to infection. It has been said frequently that inasmuch as peripheral injections will temporarily relieve pain and ergo, the lesion in major trigeminal neuralgia must be peripheral and if peripheral what more likely cause than an infection of the terminal filaments of the trigeminal nerve with an ascending neuritis. Hence oral sepsis and sinusitis, as the most common manifestations of infection in these zones, have been held by many as the responsible causative agents.

Realizing full well that the burden of proof rests on the shoulders of one who entertains the central theory as to the origin of the disease, I have never been weaned away from this hypothesis. Whether there is any justification for the central theory at least this may be said to refute the peripheral theory. First, as to oral sepsis, let me say that the elimination of this by the extraction of carious teeth or the removal of apical abscesses, *never cured* a single case of major trigeminal neuralgia. If there are any exceptions to this sweeping statement, they have never been brought to my attention in the hundreds of cases that have passed through our clinic. And if there be any force in argument by numbers, in not a single instance have I been convinced that a sinus infection was the underlying cause. And here, as with oral sepsis, when a sinus was suspected of infection the drainage of that sinus or the extraction of teeth never cured the disease.

I admit, that in a number of cases, sinuses have been drained on very flimsy evidence of infection, just as thousands of teeth have been extracted without any evidence of oral sepsis. Whenever you

hear or read of a case in which the patient is alleged to have been cured of major trigeminal neuralgia by sinus drainage you may be quite sure that the neuralgia, from which the patient suffered, is not the major trigeminal neuralgia as you and I understand the term.

I deery, as others do, the practice of extracting sound teeth *ad libitum*. Almost every day one sees a patient who has had more than one sound tooth extracted, many patients who have had all the teeth on the affected side, in upper or lower jaw, and not a few with all the teeth extracted in both upper and lower jaw on the affected side, or on both sides.

From the standpoint of etiology the "atypical" neuralgias offer an interesting field of study. As a group the clinical earmarks are very much more varied than those of the major type or the douloureux. In the latter the differential diagnosis is only exceptionally attended with doubt. Usually the diagnosis is established as the patient relates the story of his illness in the course of which, incited by talking, one of the characteristic paroxysms is easily recognized by the fixed expression of the face, the clamping movements of the jaw, the vasomotor flush, lacrymation, the appearance of great suffering. At the onset of a paroxysm the patient suddenly stops talking in the middle of a sentence, in less than a minute the paroxysm is over and he resumes his story.

In the "atypical" neuralgias the pain is continuous and frequently described as a burning or as a sense of pressure; it is deep seated, not superficial; the tissues are described as under great tension as though they would burst. The picture is quite constant; years may have elapsed since the onset but the picture is always the same; it is always a unilateral affection and the pain or discomfort is referred to very definite and unchanging zones. For the past two years, we have made a more or less intensive study of the disturbances of sensation in the trigeminal and facial nerves and cervical sympathetics, in the hope that having defined the function peculiar to each of these nerves we may find a reasonable explanation for these atypical cases. We have examined many cases after the trigeminal nerve has been paralyzed by section of the sensory root, cases of paralysis of the facial nerve alone and in combination with trigeminal anesthesia; cases after section of the cervical sympathetomy alone and combined with section of the sensory root, and a few in which all three nerves have been paralyzed. With these various combinations an unusual opportunity has been offered to study the various forms of sensation which might be attributed to these several nerve distributions.

We admit, at once without any qualification, that insofar as relates to sensation of the cutaneous or mucous surfaces pain sense, thermal and tactile sense preside in the fifth or trigeminal nerve. And without qualification we may add that we have not discovered

any objective disturbance of sensation that might in any way be related to the cervical sympathetics. We find ourselves unable to speak so definitely when we come to consider pressure sense. In the first place pressure sense must be distinguished from the sense of pain on pressure. After section of the sensory root the sense of pressure is preserved but pressure pain is lost. The patient may feel the pressure of the instrument at 4 kg. but no amount of pressure after section of the sensory root will elicit pain. Curiously enough, we have found pressure sense disturbed only when both the trigeminal and facial nerves are completely paralyzed.

Thus our observations on the sensory function of these three nerve tracts, singly and in combination, failed to give us a clue as to the explanation of these atypical neuralgias. They have, as we have noted repeatedly, one outstanding characteristic—the pain or discomfort is usually deepseated and confined to a territory that does not correspond to any particular nerve distribution. In groping about for a clue the suggestion was made that the pain distribution might correspond to some vascular zone and with this in mind one of my staff (Fay) has been studying the problem with mercurial injections of the internal maxillary and facial arteries.

Leaving these speculative considerations, we will conclude our presentation with a brief *résumé* of our experience in the treatment of the major form of trigeminal neuralgia. For many years we have relied solely: (1) Upon alcoholic injections of the second and third divisions with an occasional injection of the ganglion, and supra-orbital nerve; (2) upon the radical operation, section of the sensory root and of the two the injection method, to be successful, requires more experience than the operation. An alcohol injection to be effectual implies the injection within the nerve substance of $\frac{1}{2}$ to $\frac{3}{4}$ cc of alcohol. In inexperienced hands, many bizarre attempts have been made to inject these nerves with anything but satisfactory results and at times with harmful results. When patients have had alcoholic injections before they have come under our care, we find upon questioning that following the injection there has been no zone of anesthesia. This at once stamps the injection as "ineffectual." A successful injection implies not only the immediate relief of pain but also a zone of anesthesia in the distribution of that particular division. With these qualifications, we may assure the patient relief from six months to two years, sometimes longer.

With the understanding that there are but two and only two methods of relief, the alcoholic injection, with its transitory relief, and the radical operation, the patient is allowed to elect which of the two therapeutic procedures he will take. The patient when first seen, having had no experience with alcoholic injections, invariably chooses the injection treatment and, *vice versa*, having had 3 or possibly 4 injections, he invariably elects the operation. There is abroad still a misunderstanding of the immediate and ulti-

mate effects of the radical operation. There are many in the profession today who labor under the impression that it is disfiguring, dangerous and a more or less desperate undertaking, to be reserved as the last resort. As many of these cases of trigeminal neuralgia originate in your practice, it is only proper that you should know the truth. In the first place, as the scar is entirely concealed within the hair line, the cosmetic results are perfect. The risk of operation has been so minimized that the mortality is less than half of one per cent. We have performed over 300 major operations in the clinic; in one series of 153 cases there were no deaths and in another of 205 consecutive cases only 1 death. The operation, therefore, is neither disfiguring nor dangerous. We have modified the technique in such a way as practically to eliminate corneal keratitis as a complication. The patient must be advised that a considerable area, contracting somewhat with time, of numbness or anesthesia will follow the operation. This is unavoidable but you will never see a patient with this agonizing pain who is not willing to exchange the pain for numbness. So you should be prepared to allay in your patient the fears and apprehensions bred of misunderstandings and ignorance. Of all the forms of neuralgia, the major trigeminal form is the only one for the relief of which we have an accepted and effective remedy.

Summary. To view comprehensively the disturbances of sensation, as expressed in the neuralgias of the face, one must bear in mind three possible sources of sensory supply, the trigeminal nerve, the faeial nerve, and possibly the sympathetic. Studied phylogenetically, we find in the lower forms of animal life a close alliance between the faeial and trigeminal nerves, both as to their nuclear origin and peripheral course and distribution. Throughout the trigeminal tract there is an abundant provision for sympathetic control or association. These sympathetic connections may not be without their significance.

The varieties of sensory disturbance, as seen in the neuralgias, typify different forms of sensations, including pain, pressure, and heat. In the trigeminal nerve, as in other nerves with sensory fibers there should be, as there appears to be, disassociation of sensation. A study of patients with paralysis of the trigeminal, faeial and sympathetic singly and in combination has been made to allocate their different forms of sensation. The differential diagnosis between the atypical and typical neuralgias and especially major trigeminal neuralgia is essential in the decision for or against the major operation.

Whatever may be the cause of major trigeminal neuralgia, infection plays no part. The pain is relieved only by two measures, alcoholic injection and section of the sensory root. The latter, or major operation is almost devoid of risk. The author has performed over 300 major operations, the last 205 with only 1 death.

THE BLOOD PLATELETS IN THE LEUKEMIAS.*

BY GEORGE R. MINOT, A.B., M.D.,

AND

THOMAS E. BUCKMAN, A.M., M.D.,

BOSTON, MASS.

(From the Medical Service of the Collis P. Huntington Memorial Hospital of Harvard University.)

THE blood platelets, formed elements derived from the megacaryocytes of the bone marrow, are known to fluctuate markedly in the leukemias. In lymphatic leukemia it is characteristic to find them decreased, due presumably to a crowding out of their parent cells by lymphoid elements. The megacaryocytes are deeply implicated in the disease of the myeloid tissue known as myelogenous leukemia, so that both increased and decreased numbers of platelets occur in the peripheral blood. So many platelets and even megacaryocytes may appear in the blood stream¹ as to suggest in a rare case that the platelet-forming tissue is affected much more than the leuko- or erythroblastic tissue. In appraising the state of health of a patient with leukemia or apprehending his future, important information may be obtained from the histology of the blood, as well as serviceable knowledge from the history, physical examination and basal metabolism. A comprehensive determination of the character and numbers of white cells is of the greatest value, and a study of the state of the red cells gives useful knowledge. The blood platelets, though of less importance, are not to be neglected in determining prognosis. In the literature, except for an occasional brief note, such as given by Vogel,² statements are wanting which emphasize the information to be obtained from observation of the platelets in leukemia.

Material and Technic. During the past ten years an opportunity has been taken to study the blood platelets in some 75 cases of chronic myelogenous and 50 cases of chronic lymphatic leukemia—in many over a long period of time. These elements have been observed also in 35 cases of acute leukemia. Cases of true aleukemic lymphatic leukemia are not included. It has been possible to deduce from the accumulated observations certain conclusions regarding the platelets in these diseases so that this brief report is made.

Particularly complete and frequent observations of the formed elements of the blood were made on 35 of the patients with chronic myelogenous and 16 of those with chronic lymphatic leukemia. In

* Not only have the authors themselves made many of the determinations, but acknowledge with gratitude those made by Drs. A. H. Gunderson, L. Stern, and Miss Geneva A. Daland.

these cases of chronic leukemia blood examinations were made, as a rule, over a period of about three years, but on many the study extended over a much longer time, and in some throughout the entire course of the disease. Repeated doses of radium emanations or roentgen-rays were administered to these patients and to most of the others. There are at hand sufficient observations on the blood platelets of cases untreated and on patients at times remote from exposure to irradiation to warrant certain conclusions relative to the level of the blood platelets irrespective of treatment. For the purpose of determining the influence of the irradiation on the platelets there are many recorded observations. The immediate effects of irradiation, such as occur in the course of a few days, are not reported here. It is the more remote effects that are referred to below.

About a thousand counts of the blood platelets were made, using particularly the method of Wright and Kinnicut.³ In cases in which the influence of irradiation treatment on the platelet count was studied the enumerations were checked often by simultaneous counts made both with Pratt's⁴ and Buckman and Hallisey's⁵ method. Thomsen's⁶ technic was used occasionally, but not simultaneously with the others. These different methods yielded substantially the same results, though Thomsen's method perhaps tended to give the highest figures. Besides actual counts, estimates of the level of the blood platelets, based on inspection of properly prepared and stained blood films, yielded much data and serviceable information. There is ample justification for this procedure, as after a little experience close correlation between actual counts and estimations can be obtained, and were obtained in these cases of leukemia.

The Blood Platelets in Chronic Myelogenous Leukemia. The blood platelets in chronic myelogenous leukemia may be normal in number, increased or diminished, and in the same individual may vary markedly from time to time. However, in general, a given case shows a tendency to maintain throughout the greater part of the disease a definite level of platelets, be this within the normal or above or below the normal limits for the numbers of platelets in the peripheral blood (200,000 to 400,000 per c.mm.).

The data show that the differences in the level of the platelets in patients treated with radium or roentgen-rays are to be found in cases not receiving such treatment. Likewise changes in the numbers of these elements in a given case occur independently of irradiation, just as similar fluctuations occur in the numbers and characters of the red and white cells. However, irradiation affects the platelets and frequently can bring about desirable changes in their numbers and character, just as it alters favorably the occurrence in the blood stream of the other blood corpuscles. Irradiation may be responsible for a decrease of platelets to an undesirably

low level—by itself a sign that is important to recognize and one that necessitates caution regarding further treatment.

As a rule, we have found the platelets to be normal or slightly increased early in the disease, but marked changes in their numbers nearly always occur before death. Complete data on 35 cases irradiated at various intervals show that 26 had from a normal to a somewhat increased number of platelets (700,000 per c.mm.) during most of their illness. In nearly all there were periods of short duration, seldom over six weeks, when the platelets became much more increased above normal, while a few cases showed a transient decrease. The platelets persistently became decreased, below normal in 21 cases, beginning usually about three months, but varying from eight months to two weeks, before death. In 7 of these patients the decrease was extreme (below 50,000 per c.mm.) usually for about the last two months of life. In 3 of the 26 cases, which during most of their disease had a slightly increased number of platelets, these elements appeared in excessive numbers for a few months before death. There were 7 of the 35 patients who persistently showed during most of the course of the disease an excessive number of platelets (800,000 to 2,000,000 per c.mm.). In but 1 of these did the platelets fall to a number below normal and then in the last month of life. In some death followed a persistent rise of the platelets to enormous numbers, while in others these elements showed a tendency to fall before death, though their numbers remained well above normal. In only 2 cases did the platelets remain below normal during between 50 and 75 per cent of the course of the disease. In neither did the number of these elements ever even temporarily rise above normal, while in both the platelets decreased still more, and remained exceedingly sparse in the last two months of life.

Within rather wide limits the actual level of the platelets maintained in a given case, provided they are not very few, is of relatively little importance in forecasting the prognosis. Marked changes from this level, particularly when not transient, yield significant information. In spite of the fact that the megacaryocytes are involved in the morbid process, their frequent presence in the peripheral blood, as well as marked variations in the numbers and characters of their derivatives, the platelets may be and often are affected independently of the other marrow elements. The level of the platelets is not necessarily controlled by the status of the white cells or red cells and marked changes in the level of platelets may occur without involving the other two marrow elements. When a case first comes for irradiation treatment the white cell count is usually high and the platelets may be very few or normal and less often considerably increased. It is true, however, that when a high percentage of immature cells is present the platelets are apt to be few. It is likewise true that when the white cells

show many atypical or abortive forms, such as are prone to occur with advancement of the disease, the number of platelets is usually abnormal. Whenever there occurs through the intervention of treatment or otherwise a rise of the platelets from a definitely subnormal number, or a fall from an excessively high level to an essentially normal one, there follows clinical improvement in the patient provided the character of the leukocytes is altered in the direction of a normal blood picture. It was not unusual to see among the cases which were studied, that those with marked thrombopenia and high white cell counts soon after irradiation had flooded the peripheral blood with excessive numbers of platelets which within a few weeks fell toward normal. A shift in the platelet level toward normal values was not, however, a *sine qua non* of improvement, inasmuch as 4 cases with excessive numbers of platelets and 1 with a constant slight diminution of these elements frequently showed clinical improvement as well as a more nearly normal white cell picture, without important changes in the platelet count. A decline in the platelet count to a markedly subnormal value that was not soon restored by Nature or irradiation often preceded by not many months a fatal outcome. The temporary spontaneous decreases observed were apt to be associated with other undesirable features of the blood. A transient marked increase of platelets, not related to irradiation, exhibited by patients who usually showed a normal or slightly increased number of platelets, was apt to forecast undesirable departures from normal in the other blood elements.

An increasing number of immature white cells denotes that untoward symptoms will soon appear and that the patient's basal metabolic rate will rise. Changes in the red cells and blood platelets also may be indicative of this increased activity of the disease process. As relapse develops, the alterations in the platelets will occasionally quite overshadow those of the other blood elements. They may rise markedly and present much diversity in character, and their parent cells appear in the blood in unusual numbers. Such a picture carries the same significance as increase in immature white cells and irradiation can restore the megacaryocyte elements to normal. Under such circumstances, if irradiation is not given soon, the white cells and later the red cells will present an increasingly and markedly abnormal picture.

It is evident that a marked deviation of the platelets away from normal numbers is a bad prognostic omen. One may assume that some unknown agent in one amount stimulates the megacaryocytes and in other amounts paralyzes their functions. A marked increase of platelets is associated undoubtedly with the sharing of their parent cells in the morbid process. Though unusually high levels of platelets are to be found rather persistently in some cases while they continue in fair health, such patients will not be found to

remain so well as comparable cases with similar blood pictures, but with a more normal number of platelets. Likewise the chances for a long course of the disease become less favorable in patients with a persistently distinctly high platelet count than in those whose platelets approximate normal numbers. When extraordinary numbers flood the blood, except perhaps for very short periods of time, it indicates an impending state of affairs that is relatively serious.

Decrease of the platelets to markedly low levels is more serious than a marked increase, especially if they do not soon rise and if the total white cell count is relatively low. The thrombopenia which is often seen when many of the nucleated cells are of a character associated with a greatly increased activity of the leukemic process, for example, a high percentage of myeloblasts may be brought about by a rapid growth of immature white cells inhibiting the development of the megacaryocytes. Rarely in myelogenous leukemia a decrease of platelets is dependent upon an actual marrow aplasia. A permanent and marked alteration from the platelet level constantly shown by our patients, particularly when accompanied by increased numbers of abnormal white cells portended a relapse, which was followed usually by death in six months or less. Conversely it was generally, but not invariably, true that until such a change did take place the outlook was good for the immediate future of the patient.

Improvement in the patient's condition derived from irradiation⁷ is reflected in the blood picture. By far the most important information is to be gained from a study of the white cells, which always show changes toward normal after beneficial treatments. In an effort to obtain the maximum knowledge neither the red cells nor the platelets are to be neglected. The number of platelets, if changed markedly in the direction of normal, is a sign that is followed usually by a better state of the patient's health. On the other hand remission may occur without important changes in the numbers of platelets, while these elements, particularly after repeated irradiation, may be altered in the direction of normal without clinical improvement. However, a definite shift in the level of platelets toward normal, coincident with improvement of the white cell picture, constitutes additional evidence of effective treatment. Under such circumstances a more pronounced or longer remission is to be expected than if no change in a distinctly abnormal platelet count had occurred, or if the change had occurred for more than a short period in a direction away from normal.

The Blood Platelets in Chronic Lymphatic Leukemia. Decrease of the blood platelets is a characteristic feature of chronic lymphatic leukemia, believed to result from a crowding out of their parent cells in the marrow by the lymphocytic cells. The degree of their decrease, like the decrease of hemoglobin and red cells, serves to indicate the amount of marrow insufficiency which becomes more

marked as the disease progresses or becomes more acute. About half of 50 cases when first seen showed a distinct diminution of platelets; in the others they were within normal limits, but usually near the lower normal limits. In only 2 were they slightly above normal (550,000 per c.mm.). This patient and those with the more nearly normal number of platelets had suffered from the disease a shorter time and lived on the average distinctly longer after they were first seen than those with decreased numbers of platelets. In all of the 50 cases studied, including 16 upon whom platelet counts were made very frequently, marked thrombopenia sooner or later occurred, and there was no particular tendency in any given case to maintain a fixed platelet level. Marked reduction of these elements occurred whenever the total number of lymphocytes was excessive (over 175,000 per c.mm.), the percentage of immature forms high (over 30 per cent) or the hemoglobin level low (below 60 per cent). Whenever a few bone-marrow white cells occurred in the blood, which is the rule as the disease advances, because the bone-marrow elements become crowded out by lymphocytic foci, the platelets in turn are affected and usually fall below previous levels. There was observed no further correlation between the numbers of platelets and the blood elements.

In many cases with only a moderate diminution of platelets there occurred a rise, nearly always slight, simultaneously with reduction in the number of lymphocytes and clinical improvement. This took place both spontaneously and following irradiation. However, such improvement frequently occurred in the face of a continued sparseness of platelets, but was apt to be of a slightly less satisfactory character than when the platelets increased. In no instance did the platelets fluctuate from very low numbers to above normal and rarely even to normal, as they do in myelogenous leukemia. At times for some weeks following irradiation a rise of platelets from a level of about 175,000 per c.mm. to a little above normal occurred and this always forecasted a good state of the patient's health for at least some months. Marked thrombopenia, though always present at death, often persisted for a long time before the termination of the disease, and therefore thrombopenia cannot be taken to indicate as in chronic myelogenous leukemia a relatively rapid decline to a fatal outcome. On the other hand, a relatively rapid change to a very low level of the platelets occasionally took place, followed soon by death.

Following irradiation it generally happens that no significant rise in the platelets occurs, even when the white cell picture and the clinical condition of the patient improve. Irradiation can depress platelet formation, and in these patients, who already have a decreased activity of megacaryocytes, one must realize that this therapy can and often does suppress their functions further, leading to undesirable results. It was common in advanced cases,

especially with low white cell counts (below 30,000 per c.mm.), to observe that irradiation further decreased the platelets. When irradiation was given in the presence of marked thrombopenia significant improvement was unusual. This is in contrast to the fact that in untreated cases of myelogenous leukemia under similar circumstances improvement is usual and the platelets rise, perhaps suggesting a difference in the character of the cause of the platelet deficiency. The readily produced untoward influence of radium or roentgen-rays on the platelets in lymphatic leukemia demands that these elements be watched carefully in order to prevent, from too much treatment, more marrow depression than already exists. In general, a knowledge of the platelet count in this disease is helpful in diagnosis, in prognosis and in estimating the extent to which useful irradiation therapy can be given. All cases with a normal number of blood platelets will be found in good condition, and an increase over previous levels is a most desirable finding. However, it is surprising how often these elements may be decreased to a considerable extent without the patients being particularly ill or exhibiting purpura.

The Blood Platelets in Acute Leukemia. In both forms of true acute leukemia, from at least as soon as symptoms are evident and until death, decrease of the platelets is found always and becomes extreme, as is usually the case in acute phases of chronic leukemia. Irradiation may cause a rapid further decline. Whether, perchance, very early in acute myelogenous leukemia the platelets may be increased is unknown. That this may be true is suggested by the fact that in 5 cases of atypical subacute myelogenous leukemia, which had had their illness on the average for ten months, the platelets were somewhat increased and most abnormal in character with megacaryocytes present, although thrombopenia developed as death approached. These patients had no remissions and were not affected in any important way by irradiation. They had only slight splenic enlargement, bone pain was prominent and their white cells numbered usually about 25,000 per c.mm., composed chiefly of very immature cells.

The Relation Between the Blood-platelet Level and the Occurrence of Hemorrhage in Leukemia. It is well recognized that in the symptomatic state of purpura hemorrhagica (thrombopenic purpura) there is a marked diminution of the platelets, but that all symptomatic hemorrhagic conditions are not related to this defect. In about 50 per cent of our cases of chronic myelogenous leukemia, for whom records of the whole course of the illness are complete, there developed petechiæ, sometimes with other purpuric lesions. The petechiæ were often few, but occasionally coincident external or internal hemorrhages occurred with a continued paucity of platelets. The purpuric manifestations usually appeared toward the close of the patient's illness. In some cases the symptom was

evident a few years before death and disappeared as the platelets rose after irradiation. Hemorrhages also occur in this disease when the platelets are normal as well as when they are much increased (1,500,000 per c.mm.). Under such conditions it is to be emphasized that petechiæ have not been seen, but rather bleeding in the form of ecchymoses from trivial trauma, epistaxis, and bleeding from a surgical operation, such as removal of a tooth. Such blood loss occurred in about 25 per cent of the cases and apparently always at a time when deviations from normal in the white cell picture were marked. Similar hemorrhages occur in erythremia and are considered related to the altered physical state of the polycythemic blood. A comparable condition due to the leukocyte increase probably exists in leukemia. Hemorrhage in chronic myelogenous leukemia may result also from the leukemic infiltration of different organs; for example, the kidneys, leading alone or when combined with the effect of a low platelet count to hematuria, usually slight, as occurred in 15 per cent of 110 cases.⁸

In chronic lymphatic leukemia purpura in the form of petechiæ and ecchymoses is observed much more frequently, usually more extensively and for a much longer time than in chronic myelogenous leukemia. This is to be expected because thrombopenia is a feature of the disease throughout a great part of its course. Bleeding from mucosæ and into organs is not uncommon. The hemorrhagic manifestations of thrombopenia are present nearly always a few weeks, rarely for but a few days, before death. Nevertheless petechiæ and ecchymoses in varying amounts are seen quite often during many months and even as long as two years before the termination of the disease. We have seen a few cases that have had purpura for many years before signs of leukemia became obvious. The purpuric lesions were present a year before death in at least 10 per cent of 80 cases which had had their disease, on the average, for 3.45 years.⁹ When irradiation is given in the presence of outstanding purpura, always occurring in this disease with profound thrombopenia, symptomatic benefit is very unusual, quite in contrast to the results observed in chronic myelogenous leukemia. In spite of the frequency of a decrease of platelets in chronic lymphatic leukemia, many cases exhibited no purpura when the platelet count had fallen and remained below a level (60,000 per c.mm.) at which purpura usually is expected, though it developed sooner or later as death approached. In fact, one of the striking and unexplained relationships between the numbers of platelets and spontaneous bleeding is that their actual decrease does not indicate the amount of hemorrhage in different cases or in the same case at different times. Hemorrhages never occurred in the cases of lymphatic leukemia when the platelets were normal in numbers. Blood loss due wholly or partially to leukemic infiltration does occur in lymphatic as in myelogenous leukemia.

In acute leukemia it is the rule that all the manifestations of symptomatic purpura hemorrhagica develop, and often to an intense and distressing degree.

Summary. A study of the blood platelets yields useful knowledge for guiding treatment and appraising the state of health of a patient with leukemia. In chronic myelogenous leukemia the numbers of these elements may be normal, enormously increased, or greatly diminished, and in chronic lymphatic and acute leukemia it is the rule to find them below normal. The fluctuations that occur in the numbers of blood platelets are discussed. Petechiæ and other hemorrhages associated with decrease of blood platelets are common, and hemorrhages, but not petechiæ, may occur in chronic myelogenous leukemia when the platelets are much increased.

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A SUMMARY OF THE EFFECTS OF EXTERNAL HEAT UPON THE HUMAN BODY.

BY RALPH PEMBERTON, M.D.,

PHILADELPHIA.

THE application of external heat to the human body constitutes one of the oldest forms of treatment of which there is any record. Heat was used extensively by the ancients in the form of hydrotherapy and has since been widely applied as hydrotherapy alone or in such accessory forms as hot-mud baths, turkish baths, hot packs, vapor baths, hot-air baths and electric-cabinet sweats. It has been increasingly applied to a large variety of diseases.

Although the undoubted benefits from the use of external heat have long been recognized, but little attempt has been made to understand the *modus operandi* of the processes concerned. The therapeutic application of heat has, for the most part, been left to uncritical observers, and it is common knowledge among the laity as well as the profession that damage as well as benefit often accrues, probably as the result of misapplication and undue zeal. There are

in this country and Europe establishments whose employment of these measures is not highly discriminating, although at the better-known resorts the supervision of a physician is required.

It has therefore long been important to ascertain what transpires during exposure of the body to external heat, with the double aim of learning something of the pathology underlying conditions thus influenced for the better and also of determining the limitations and dangers in the methods themselves. The past three or four years have been productive of data of value which, however, are scattered through journals not necessarily widely read by the general medical public. It is chiefly to the general medical public however, that the information recently acquired is of value, and it is therefore the purpose of this article to endeavor to correlate the various lines of work on the subject and to state briefly the changes that occur so far as our knowledge permits.

In conjunction with his associates, the writer has for some years been studying the changes accruing from exposure of the body to external heat in the form of radiation from electric lamps, the so-called "bake." Within limits, the principle involved is much the same whatever be the source of the heat, and the electric cabinet bake lends itself to study more readily than do other and more cumbersome processes, some of which require elaborate equipment. Bazett and Haldane¹ showed that subjects immersed in water at a temperature of 38° C. experience a rise in the body temperature, accompanied by hyperpnea, sometimes a sensation of giddiness, a fall in the alveolar carbon dioxide and an alkaline sweat. Haggard,² in experimenting upon himself in a bath at 40° C. for twenty minutes, observed similar changes in the alveolar air, together with a drop in the CO₂ content of the blood. As he observed no fall in the carbon-dioxide combining power he postulated a lowering of the hydrogen-ion concentration of the blood.

Pemberton, Hendrix and Crouter³ observed an analogous fall in the alveolar CO₂ during exposure of the body to an electric cabinet bake, with a rise in the CO₂ after the bake. The same writers also conducted a series of observations upon the oxygen content and capacity of the venous blood, and found that during the course of an electric bake the oxygen content rises very appreciably although the capacity is but little altered. This rise in the percentage saturation of the blood with oxygen is presumably due to the increased rate of bloodflow.

The phenomenon of sweating which accompanies these measures has been regarded as perhaps the chief desideratum and certainly one of the criteria of successful administration of this form of therapy. In general, the benefit arising from sweating has been ascribed to an elimination of nitrogenous substances and possibly salts. This conception undoubtedly finds support in cases of nephritis where the blood nitrogen is high and removal of part of

it through the sweat in the form of urea can be demonstrated. This explanation, however, has been assumed as adequate in other conditions where the nitrogenous elements of the blood are not concerned. Medical literature is full of references to the "elimination" achieved by these measures, but there have been few suggestions and fewer data to indicate what the substances eliminated might be.

It has long been recognized that carbon dioxide is eliminated to some degree in the sweat. Thus, at a temperature between 29°C . and 33°C . the CO_2 output is about 35 gm. per hour, but when the external temperature rises above 33°C . the output increases; at 34°C . it may be doubled and at 38.5°C . it may be more than trebled (Starling⁴). There is a paucity of data in the literature upon sweat, however, and the changes which it undergoes, if any, during exposure of the body to heat. The data bearing upon the reaction of the sweat have been contradictory, and Pemberton and Crouter⁵ undertook a study of the hydrogen-ion concentration of the sweat during electric bakes. It was observed that the sweat under these circumstances in normal individuals has an average initial reaction or pH of 7, which is very slightly on the acid side of the blood reaction, although there may be departures either way. The first sweat to appear may thus be acid, alkaline or neutral, but whatever the initial reaction, it invariably undergoes a change towards the less acid or more alkaline range which continues progressively during the course of the bake, generally becoming markedly alkaline. The only exceptions to this so far observed have occurred in a few cases of arthritis and one of scleroderma whose sweat tended to remain very acid throughout—around 4.6.

It was at first thought that the change in the reaction of the sweat might be referable to a lower acidity brought about in it by loss of carbon dioxide from it, especially as it was found that the carbon-dioxide content of the air in a rubber bag placed around the arm increased more or less parallel with the drop in acidity of the sweat elsewhere. Further observations by Cajori, Crouter and Pemberton⁶ showed that this apparently is not the mechanism concerned. On determining the so-called carbon-dioxide absorption curves of the blood before and during the bake it was discovered that there is a change in their level, a rise, which means that as the bake progresses the blood is able to absorb more carbon dioxide. More alkali becomes available, or, in other words, the blood becomes more alkaline. Following this change the urine generally becomes more alkaline also. These observations were further controlled by studying the hydrogen-ion concentration of the blood directly by means of Cullen's colorimetric method and comparable results were obtained, the hydrogen-ion concentration or acidity decreasing. Since the completion of these studies Koehler⁷ has published analogous changes during the hyperpyrexia of

fever and also as the result of a rise in body temperature following extremely hot baths. He measured the pH of the blood electrometrically by means of the calomel electrode so that in principle the same results have been arrived at by several methods and different observers.

It therefore appears that during the therapeutic application of external heat, not to mention the more severe applications which most of the above workers employed, there occurs a loss of acid from the body which results in a relatively increased alkalinity of the fluid tissues. This acid is mainly CO_2 and it makes its escape chiefly through the lungs, although there is also a considerable output through the urine,⁸ and also through the sweat as above described. Other acids are also eliminated, and Cajori, Crouter and Pemberton⁹ have shown that in the sweat lactic acid is one of them, although the total amount is not great. The result of this loss of acid from the body is that the blood becomes relatively more alkaline, and in order to maintain its equilibrium it eliminates the excess alkali through the urine and sweat.

It is, therefore to be appreciated that very profound changes in the acid-base equilibrium of the blood follow even what has been regarded as a mild therapeutic measure. The change in the reaction of the blood was in one case from a pH of 7.26 to 7.52. It is not surprising, therefore, that so many undesirable consequences have followed the use of hydrotherapy and external heat when these measures are carried out in a wholesale way. In addition to the change in the blood reaction, which must be resisted and compensated for, there is the previously recognized rise in the general metabolism from the increased bloodflow, and Gram¹⁰ has recently shown by observations on the hemoglobin that the blood becomes more concentrated. The full consequences of alkalosis are not entirely known, but one of the baneful effects is the induction of tetany.

It is believed that the general nature of the above reaction should be understood by all persons who concern themselves with the application of external heat to the human body in order that there may be a more intelligent appreciation of what is to be accomplished and of the possible dangers. As a corollary to the above, it is interesting to note that the benefit of hot packs and sweats in nephritis may be due not solely to the elimination of nitrogenous substances, as so long believed, but also, in part at least, to the relative alkalosis brought about by the elimination of acid radicals, chiefly CO_2 . The influence of these processes upon the acidosis of nephritis or other conditions is obvious.

Summary. Exposure of the body to the therapeutic application of external heat results in a heightened bloodflow, an increased metabolism and in the elimination of acids, chiefly carbon dioxide which escapes through the lungs, urine and sweat in the order of -

magnitude named. This leaves an excess of alkali in the blood which then changes its reaction, becoming more alkaline. In the compensatory effort to meet this situation, the excess of alkali is eliminated through the sweat and urine. The profound nature of the changes induced by these measures is clearly indicated, and explanation is afforded of some of the baneful consequences which follow their uncritical use. If carried to extremes tetany may result. The available evidence indicates that part of the benefit of the sweat process in some forms of nephritis is due to loss of acid substances from the body, with consequent benefit to the acidosis frequently accompanying renal disease.*

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DYSTROPHIA ADIPOSEGENITALIS, WITH ATYPICAL RETINITIS PIGMENTOSA AND MENTAL DEFICIENCY—THE LAURENCE-BIEDL SYNDROME.

A REPORT OF FOUR CASES IN ONE FAMILY.

BY SOLOMON SOLIS-COHEN, M.D.,

AND

EDWARD WEISS, M.D.

PHILADELPHIA.

THE purpose of this report is: (1) To place on record the histories of four members of one family who present overgrowth of fatty tissue and undergrowth of the genitalia—the so-called Froehlich syndrome—associated with other abnormalities of development, including retinal atrophy with pigmentary filtration; (2) to call attention to previous reports of cases so closely parallel to ours, that we may, with Biedl and Raab, look upon the condition as a definite syndrome.

Catherine L., a girl of Italian parentage, aged seventeen years, was admitted to the medical ward of the Jefferson Hospital, Octo-

* The work of the writer and his associates constitutes part of a study on arthritis in collaboration with Robert B. Osgood, Boston.

ber 22, 1923. She was delirious and had a high fever. The cause of this was determined to be acute pyelitis. Her temperature soon became normal, but after a few days rose again, and again subsided; and thus during November and December she continued to have flights of fever lasting for several days. Finally, shortly after the New Year, her temperature remained constantly normal, all evidences of pyelitis having disappeared. During the period of this illness we had noted with interest the girl's strange appearance, odd behavior and remarkably poor vision; and during an afebrile interval had had her eye-grounds examined by one of our colleagues (Dr. Heed), who recognized the condition present; but not until the acute infection had entirely subsided, did we deem it opportune to make a thorough study.

Questioned concerning her family, Catherine informed us that there were 8 children; 3 others, like herself, fat and with poor vision; 4 thin, and with good vision. The 7 were brought to the dispensary and studied; the father and mother were seen at their home. The photographs of the affected children are reproduced in Figs. 1, 2, 3 and 4.

The father, a day laborer, aged sixty years, was born in Italy, about 100 miles north of Rome, in a healthy district where no endemic disease prevails. He was the first born of a family of 6, 4 boys and 2 girls, all of whom are living and well. Neither he nor his brothers, sisters, or parents, suffered from known visual defect. None has exhibited marked adiposity, polydactylism, deafness or idiocy; nor, insofar as he could inform us, were these phenomena present in other relatives. This, however, may indicate merely ignorance of family ramifications, or the peasant's failure to take notice, and does not necessarily imply absence of such dystrophies in previous generations, or in collateral lines.

The same holds true as to the mother, who is fifty-two years of age, and has no known kinship with her husband. She was born in the same district in Italy (the Abruzzi); was fifth in a family of 6, 1 boy and 5 girls. She married when twenty-one years of age, and in addition to her 8 living children had 1 miscarriage. This occurred without known provocation, in the second or third month of her second pregnancy. Both father and mother have always been healthy, and in both the blood Wassermann reaction is negative. Of their 8 children 4 are abnormal, as indicated in the following list:

- Male, aged twenty-five years, normal.
- Male, aged twenty-one years, *abnormal*.
- Female, aged nineteen years, normal.
- Female, aged seventeen years, *abnormal*.
- Female, aged fifteen years, *abnormal*.
- Female, aged thirteen years, normal.
- Male, aged eleven years, *abnormal*.
- Female, aged nine years, normal.

We might add, as to the last named, that, both physically and mentally, she is uncommonly alert, acting as shepherdess to the abnormal flock on their visits to the hospital.

Detailed description of the affected members of the family follows:

Case Reports. CASE I.—Catherine (Fig. 1), the child who first engaged our attention, had a normal birth and seemed a fat, normal infant, except for six toes on the right foot, one of which was later amputated. Dentition began at the fifth or sixth month; she began to walk at one year and to talk at two years. She had measles and

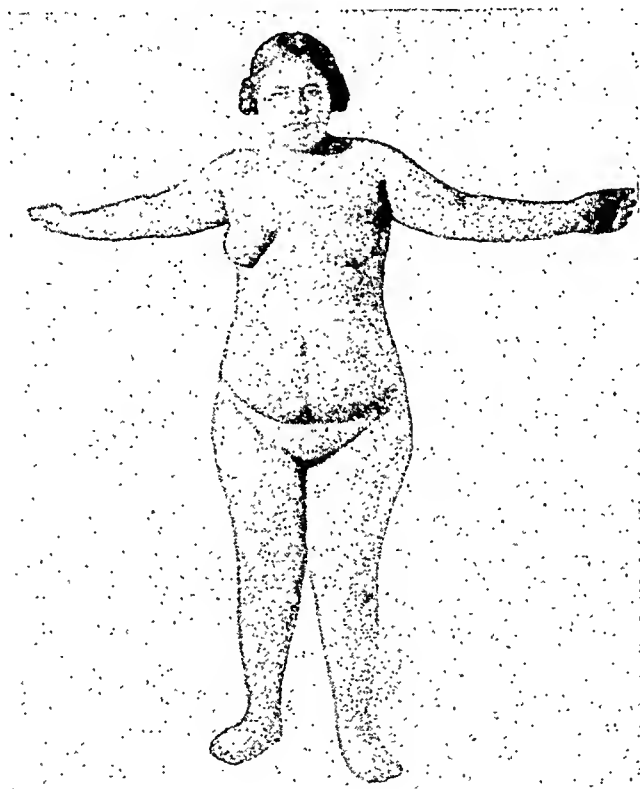


FIG. 1

whooping-cough, from which she made good recovery. Diminution of vision became noticeable at about the age of fifteen years, and has been progressive since. She did not menstruate until she was about seventeen years of age (May, 1923), and then not again for nine months. One month prior to her admission to the medical service she had been brought to the hospital with a diagnosis of acute appendicitis, but at operation an ovarian cyst, with twisted pedicle, was discovered.

Physical examination in the medical ward, after she had recovered from the attack of pyelitis (January, 1924), showed a very stout, short girl, with high color and an ordinary amount of coarse

black hair. She weighed 152 pounds. Her height was 144 cm.; her span, 142 cm.; from symphysis to sole she measured 71 cm., and from symphysis to vertex, 74 cm. Her expression was staring, but not vacant. She found her way with difficulty, bumping into objects as she moved about.

The face is round, the nose small, the teeth normal, the palate high arched, the tonsils large and cryptic; the neck is short and chunky and the occiput is sheer. There is no adenopathy. The *thyroid gland* is palpable, but not enlarged. The breasts are large and pendulous. *Adiposity* is marked and generalized, but is especially of the mammary, mons and girdle type. The hair growth in the axilla and pelvic regions is scanty. It has the usual feminine distribution over the mons pubis. The heart and lungs seem normal. Abdominal examination is negative, except for two scars, one in the appendiceal region and one in the midline. The arms and legs are fat and shapeless, the thighs being especially thick. There is a slight degree of genu valgum. The hands and feet are short, thick and broad. The fingers, although short, are tapering, while the toes are chunky. The nails present nothing of special interest, but are on the whole, poorly developed. Reflexes are normal. *Mentality* is markedly deficient, although she answers questions with short, snappy replies, and has a sort of infantile wit. Her vocabulary is limited, but there is no difficulty in speech. She is happy, is easily amused and laughs a great deal.

Eye examination (H. F. Hansell) shows "partial night blindness; fields limited concentrically to a small area around the fixation point; pupils dilated, left a trifle larger; no reaction to light or convergence; convergence almost in abeyance; no muscular paralysis; a few small vitreous opacities, one adherent to the posterior lens surface on right; optic nerve and retina partially atrophied; retinal vessels diminished in caliber and length; pigment spots scattered throughout each fundus. Diagnosis, 'atypical retinitis pigmentosa.'""*

Ear examination shows a bilateral chronic catarrhal otitis media.

Laboratory examination: The urine output was about 1 liter in twenty-four hours; examination negative. Blood count shows: Hemoglobin, 57 per cent; red blood cells, 3,690,000; white blood

* In a report of these same patients, read before the Oxford Congress of Ophthalmology in July, 1924, by H. F. Hansell, he makes the suggestion that a better term than retinitis pigmentosa for this condition would be "optic nerve and retinal atrophy associated with pigment filtration," as being more nearly descriptive of the clinical and pathological process. W. H. Wilmer (Arch. Neurol. and Psychiat., 1924; 12, 137), in a paper entitled "Hereditary Factors in Optic Atrophy and Retinitis Pigmentosa" suggests the term "pigmentary degeneration of the retina;" or would accept Collins's suggestion of "abiotrophy of the retinal neuro-epithelium," perhaps simplified as "retinal abiotrophy." ("Abiotrophy," a term introduced by Gowers, is defined by Collins as "The premature failure of the inherent vitality of a tissue, giving rise to impairment or destruction of certain functions before the death of the organism as a whole.")

cells, 10,000; differential count normal. Blood-pressure averaged 110/70. Blood Wassermann was negative. Basal metabolism was -19. Sugar-tolerance tests showed a deficient response to the ingestion of 1.75 gm. of glucose per 1 kg. of body weight.

Gynecological examination shows external genitalia normal, except for the sparse growth of pubic hair. Examination of the internal genitalia discloses an infantile uterus.

Roentgen-ray study fails to demonstrate the presence of the thymus gland, nor does it show any changes in the long bones or their epiphyses, or the bones of the hand or wrist. The sella turcica was reported as "within normal limits in size." The dorsum is perhaps somewhat higher than common. Our general observation however, and the careful studies of Schaeffer and de Schweinitz reported in the latter's Bowman Lecture, make us chary of drawing conclusions from sellar shadows.

Pituitary and thyroid therapy produced no change in weight, in mentality or in temperament. The girl said she "saw better," but there was no objective confirmation of this, and suggestion was not absent. Moreover, there was hospital care and rest as a general upbuilding influence. The menses appeared for four days in February, 1924 (nine months after the previous menstruation), and again in March and April. This seemed, at least, to be the result of the endocrine therapy.

CASE II.—Nicholas (Fig. 2), aged twenty-one years, the oldest of the abnormal children, is very much like the girl just described. He is a big laughing boy, with high color and a sparse growth of hair in the beard region. He weighed 221½ pounds and measured 160 cm. in height; 78 cm. from the symphysis to sole, and 88 cm. from symphysis to vertex. His span was 159 cm.

At birth he seemed a normal child, except for six toes on the right foot. Dentition began at six months, and he began to walk when one year, and to talk when two years, of age. He had measles and scarlet fever in childhood, from both of which he made good recovery, and he has not been sick in bed since. He says, and his parents affirm, that he has been fat all his life. At the age of sixteen years he noticed some failure of sight, and this has grown progressively worse. He works as a newsboy at night, making his way to and from his stand with great difficulty, on account of his poor vision. Otherwise he is in excellent health.

Physical examination reveals *adiposity* chiefly of the mammary, mons and girdle type. He has some degree of genuvalgum. His hair is black, coarse and thick. The eyes are almost constantly moving, the nose is small, the ears are thick and set close to the head, the teeth are good, the palate is high arched and the tonsils are large. The back of the head is straight with the neck, which is short and thick. The *thyroid gland* is palpable, but not enlarged.

The heart and lungs are normal; abdominal examination is negative. The axillary hair is rather sparse; pubic hair is about normal in amount and distribution. The *penis* is very small; the testes, however, seem normal in size. The hands and feet are broad and thick. There is no adenopathy, and the reflexes are normal. He, too is *mentally* deficient, but seems more intelligent than his sister. He counts in "twos," probably because his papers sell for two cents each. He is of a very merry disposition, is easily amused and laughs readily.

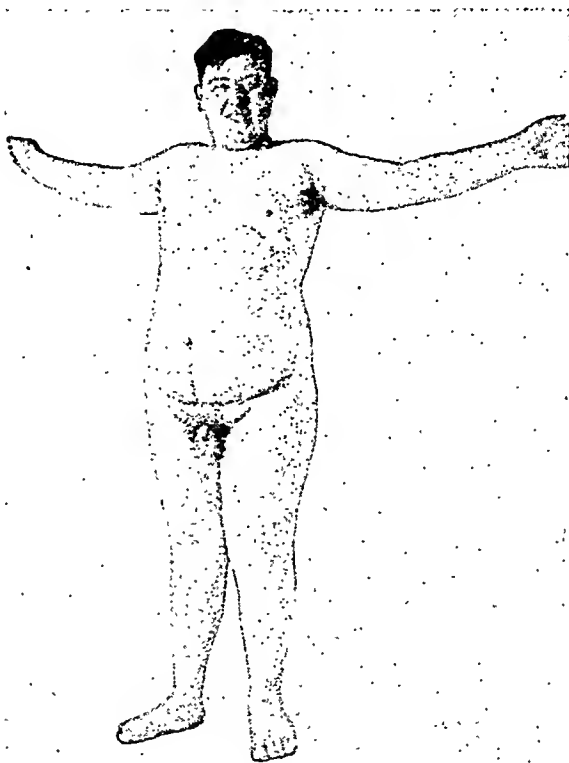


FIG. 2

The *eye report* is as follows: "Highly myopic and astigmatic; night blindness, increasing each year. There is a rapid, jerky vertical and rotary nystagmus, augmented by attempts to see objects held close to the eyes. The optic nerves are atrophic; the arteries and veins are reduced markedly in size. Pigment spots and a few 'bone corpuscles' are scattered throughout the fundi. The fields are limited to a small area around the fixation point. Convergence is deficient. Pupils are equal and react." (Hansell).

Laboratory studies are as indicated in the accompanying chart which gives the principal data of our records arranged in tabular form. Basal metabolism was normal; sugar tolerance slightly reduced.

TABULATION OF THE PRINCIPAL DATA OF OUR RECORDS.

	Nicholas, 21 yrs.	Catherine, 17 yrs.	Anna, 15 yrs.	Joseph, 11 yrs.
Dentition	5-6 mos.	5-6 mos.	6-7 mos.	6-7 mos.
Walking	12 mos.	12 mos.	16 mos.	11 mos.
Talking	2 yrs.	1½ yrs.	2 yrs.	15 mos.
Poor vision noticed	16 yrs.	15 yrs.	13 yrs.	10 yrs.
Present weight, pounds	221½	152	121	110
Height, cm.	160	144	136	136.5
Span, cm.	159	142	138½	129
Symphysis to sole, cm.	78	70	67	65
Symphysis to vertex, cm.	82	74	69	71.5
Temperature, pulse and respiration	Normal	Normal	Normal	Normal
Urinalysis	Negative	Negative	Negative	Negative
24-hr. output, in cc	900-1000	1000	800	1000
Blood-pressure	130/90	110/70	120/85	110/60
Blood count	Normal	Secondary anemia	Normal	Normal
Wassermann	Negative	Negative	Negative	Negative
Basal metabolism	-3	-19	-29	-21
Sugar tolerance 1.75 gm. per kilo body weight (per cent, blood sugar):				
Before	0.118	0.098	0.116	0.101
½ hour	0.246	0.176	...	0.166
1 hour	0.268	0.199	0.190	0.125
2 hours	0.163	0.202	0.135	0.109

Roentgen-ray studies show normal long bones, wrist and hand; the sella turcica is reported as "slightly smaller than the average." The posterior clinoid is high. No thymus shadow can be made out.

Endocrine therapy, pituitary and thyroid, over a period of eight months, has had no apparent effect on this boy.

CASE III (Fig. 3).—Anna, aged fifteen years, is a dull-looking, shy girl, excessively developed for her age. She weighed 121 pounds. She measured 136 cm. in height, 67 cm. from symphysis to sole and 69 cm. from symphysis to vertex; her span was 138½ cm.

She appeared to be a normal child at birth. Unlike the two whose histories have been detailed, she did not have an extra toe. Dentition occurred normally; walking and talking were somewhat delayed. She had measles, but made a good recovery, and has had no other illness. Her general health has been excellent. Dimness of vision was first discovered at about the age of thirteen years; it was noticed in school that she could not follow a straight line in writing. Menstruation began when fourteen years of age, and has always been regular.

Physical examination: Her *adiposity* is of the girdle, mons and mammary type; the mammae are especially large. Her hair is straight, black and coarse; the teeth are normal; the palate is high and narrow; the tonsils are large. The *thyroid gland* is palpable, but not enlarged. Heart and lungs are normal; there is no adenopathy, and the reflexes are normal. The external *genitalia* are normal, but rectal examination discloses an infantile uterus. This

child, too, is deficient *mentally*, but does not seem to share in the exceptionally happy disposition shown by Nicholas and Catherine. Allowing for her mental hebetude, however, her mirth reactions seem about normal.

Roentgen-ray study of the sella turcica shows "floor rather uneven and posterior clinoid process inclined slightly backward." No thymus shadow can be made out. Roentgen-ray of the long bones, wrist and hand is normal.

Laboratory examination: A sugar-tolerance test showed a slight deficiency in her ability to handle glucose. The basal metabolism was -29 .

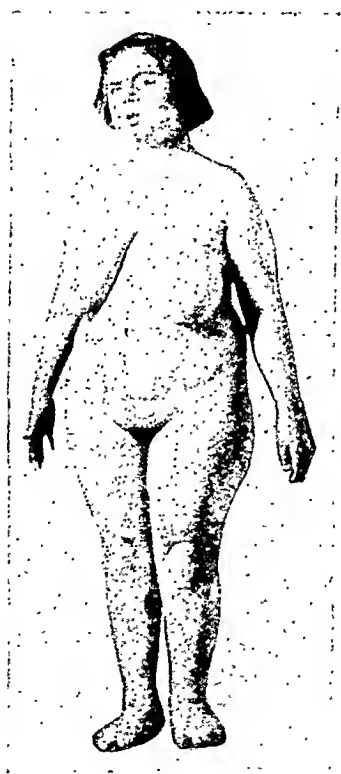


FIG. 3

The *eye report* shows: "Media clear; numerous round, pigmented spots throughout the peripheral retina. The nerve is of fairly good color; the vessels are contracted. There is partial optic nerve and retinal atrophy. The fields are concentrically contracted. Diagnosis, early retinitis pigmentosa." (Hansell.)

Hormone therapy seemed without effect on this girl.

CASE IV (Fig. 4).—Joseph, aged eleven years, the youngest of the abnormal children, is a dull-looking, fat boy, very much like the others. He weighed 110 pounds. He measured 136 cm. in height; his span was 129 cm.; from symphysis to sole he measured 65 cm., and from symphysis to vertex $71\frac{1}{2}$ cm.

He was apparently a normal infant (no extra toes or other stigmata); dentition, walking and talking occurred at the common times. He had diphtheria at the age of ten years, and made a good recovery. Otherwise he has always been in good health. His dimness of vision, like his sister Anna's, became noticeable in school about one year ago, when he experienced considerable difficulty in reading and writing. Like Anna, he is *mentally* deficient, without marked euphoria.

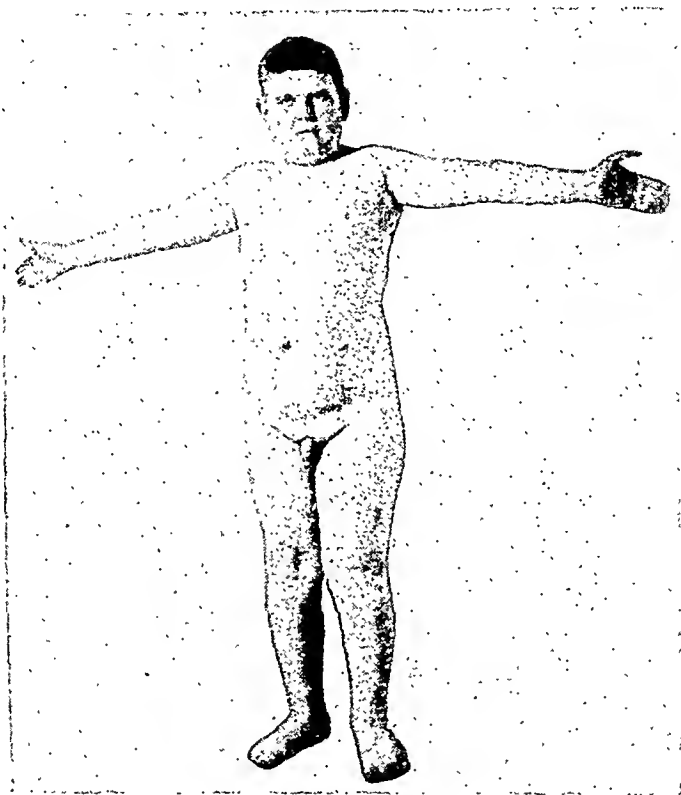


FIG. 4

Physical examination shows an obese boy, with *adiposity* a little more marked in the girdle, mons and mammary regions. Like the other children, he has a high-arched palate and enlarged tonsils. His hands and feet are thick and chubby. *Genital* development seems fair for a boy of his age. There is a moderate degree of phimosis.

Eye examination shows the following: "A decided optic nerve and retinal atrophy. There are a few pigmented spots scattered throughout the periphery of each fundus. No myopia; no nystagmus. Patient too stupid to take visual fields. Diagnosis, atypical retinitis pigmentosa." (Hansell.)

Roentgen-ray study of the sella turcica, thymus and bones revealed nothing abnormal.

In laboratory study, reaction to sugar-tolerance tests was normal; basal metabolism, -21.

Hormone therapy seemed without effect.

Summary of Cases. Four of 8 brothers and sisters of Italian parentage, exhibit marked adiposity with mental deficiency, genital dystrophy and diminution of vision. Two of the abnormal children show polydactylism. The eye-grounds (H. F. Hansell) show atypical retinitis pigmentosa. The fat distribution is largely of the girdle, mons and mammary type. An hypophyseal lesion cannot be proved. Roentgen-ray examinations of the sella region do not show conclusive changes. No anomaly of osseous development is found. Sugar-tolerance tests do not indicate pituitary disease. Basal metabolism was below normal in 3 of the children. Both parents and children gave negative Wassermann reactions. The thyroid glands are palpable and within ordinary limits of size and consistence. There is no lymphadenopathy, and no history of rickets.

Family history of marked adiposity, visual defect, polydactylism, deafness or idiocy could not be obtained. The four unaffected children seem entirely normal; one, indeed, is uncommonly bright and active. Hormone therapy (pituitary—thyroid) seems to correct amenorrhea in the older girl, but otherwise was without effect on any of the children. Subjective improvement in the sight of the elder girl may have been the result of hormone therapy, but may with equal probability be referred to suggestion, or to the general improvement of nutrition attending hospital care.

Review of Similar Cases. A survey of the literature of retinitis pigmentosa brought out the following remarkably similar group reported by J. Z. Laurence and R. C. Moon, in 1866, under the title, "Four Cases of Retinitis Pigmentosa Occurring in the Same Family, Accompanied by General Imperfections of Development."¹ These authors describe the case of Marian T., aged seven years; 3 feet 8 inches in height, a flat-featured, heavy looking child with light auburn hair and gray irides. Her sight had been defective for two years. There was night blindness and slight lateral oscillation of each eye, combined with a very imperfect power of fixation. Ophthalmological examination revealed retinitis pigmentosa.

No hereditary tendency could be traced, nor were the parents related by blood. There had been 10 children in all; 2 died in infancy, 1 of smallpox and the other of consumption. Both the father and mother were active, intelligent and well built, with no imperfection in sight. The following description of the children was given by the parents:

Richard, aged twenty-four years, a fine young man, healthy in every respect.

Arthur, aged twenty-two and a half years, also a fine young man, healthy in every respect.

Harry, aged twenty years, *afflicted*, and has bad sight.

Ferdinand, aged eighteen years, *afflicted*, and has bad sight.

Charles, aged fifteen years, *afflicted*, and has bad sight.

Edwin, aged thirteen years, healthy in every respect, and very sharp at learning.

Willie, aged nine years, healthy in every respect.

Marian, aged seven years, a very quiet, slow child, *afflicted* with bad sight.

To this, the authors of the report add their observations, which we give in abstract:

Harry, aged twenty years, is short for his age, measuring 5 feet $3\frac{1}{2}$ inches. He walks with a slouching gait, "as if he were tipsy," and appears to have hardly sufficient power to drag his legs; there is rather deep depression between the scapulæ. The curve of the lumbar vertebræ, however, is very considerable, causing the trunk to be thrown forward from the hips and the buttocks to be more prominent than usual. The lower extremities are short and the muscles flabby. He has a stolid, heavy countenance, and appears to be rather obtuse and unintelligent. He answers question slowly, but with tolerable accuracy.

Eye examination shows the power of fixation imperfect and the eyes rather continuously moving from side to side. The eye-grounds show retinitis pigmentosa.

Ferdinand, aged eighteen years, is 4 feet $6\frac{1}{2}$ inches tall. He is a fat, heavy-looking boy, and, like Harry, he walks with a slouching heavy gait, dragging his legs from the hips. Eye-sight was first noticed to be defective at the age of six or seven; it has become progressively worse ever since. Eye examination shows retinitis pigmentosa.

Charles, aged fifteen years, is 4 feet 4 inches tall. He is dull and and inanimate, and walks with a slouching gait, but not to the same extent as his two brothers. Sight has been defective since one year of age. Eye examination shows retinitis pigmentosa.

The organs of regeneration are also strikingly implicated in the general want of development. There are no signs of rickets, scrofula or syphilis.

We quote the closing paragraph of this noteworthy and philosophical report. (The italics are ours.)

"In calling these cases by the name of retinitis pigmentosa, we have been guided by usage rather than by the intimate nature of the cases. Had we taken the latter view, we would rather have entitled our paper, 'Four Cases of Arrest of Development and Atrophy of the Eye,' or we might even *have gone a step further in the generalization of our title, as the arrest of development was by no means confined to the eye, but affected several other organs of the*

body. In this latter point of view, and more especially when we regard the mental faculties, these patients may in a certain sense be compared with *cretins* in a mild degree. In no member of the entire family was there any bronchocele."

SUMMARY OF REMARKABLY SIMILAR FAMILY GROUP REPORTED BY LAURENCE AND MOON IN 1866. Four of 8 brothers and sisters of healthy parents, showed retinitis pigmentosa, adiposity, genital dystrophy and mental deficiency. Three of these likewise showed imperfections of bony and muscular development leading to defective gait. There was no sign of rickets, of scrofula or of syphilis. The authors recognized that the retinal changes were but part of a general developmental failure and that, especially in view of the mental condition, these persons could be, not inaptly, compared to *cretins*.

SIMILAR CASES RECOGNIZED AS A SYNDROME BY BIEDL. Raab, in the course of a very careful study from Biedl's Clinic, emphasizes the occurrence of "a syndrome, perhaps familial, hitherto scarcely known, of (1) optic atrophy with pigmentary degeneration similar to retinitis pigmentosa, (2) polydactylism, (3) obesity and (4) genital hypoplasia." Except for its failure to include mental deficiency, this description agrees with our cases, as well as with those cited from Laurence and Moon. Biedl, however, when in Philadelphia in the spring of 1924, saw our patients, and in confirming our opinion of the identity of the syndrome with that which he had described, included the mental phenomena. Indeed, he laid stress on this feature as evidence of a cerebral, rather than a hypophyseal origin of the disorder. We accordingly propose to call it the Laurence-Moon-Biedl syndrome, in acknowledgment of its original observers and of its rediscoverer.

Biedl's cases, reported in abstract in 1922,² are recorded in detail by Raab.³

BIEDL'S CASES. The family history was negative. The mother had 6 normal births and 1 miscarriage. The order of births was as follows:

Girl, aged twenty-two years, first born, *affected*.

Boy; had *polydactylism*; died at age of two years, of pertussis.

Girl; had *polydactylism*; died at age of three weeks.

Boy, normal; died at age of nine months.

Boy, aged sixteen years, *affected*.

Boy, aged fourteen years, normal.

CASE I.—A girl, aged twenty-two years, was a stout child. She has had poor vision in twilight since childhood, and in the last year she has had marked diminution of vision. Obesity has increased since the age of sixteen years. Menstruation began at twenty-one years; the flow was scanty and irregular, appearing

only four times, and has not appeared for one year. She has a wide head, and the head and neck are vertical. The hair on the head is coarse, and there is some hair on the cheeks, chin and upper lip. Axillary hair growth is poor, but there is considerable hair over the pubic region, distributed in masculine fashion. The skin is rough and dry, the face ruddy, and the skin of the chest and extremities is mottled. There is adiposity, especially of the breasts, abdomen (limited by a deep furrow at the mons pubis) and hips. The thighs are massive, but the extremities otherwise are less involved in the adiposity. The hands are short, the joints wide, and the fingers end in knobs. The feet are short and broad and there is genuvalgum of a moderate degree. There is an extra toe on the outer side of the left foot, and syndactylism between the second and third toes of the right foot.

The eyes show a slight divergent strabismus; pupils react poorly to light and convergence. The eye-grounds show retinitis pigmentosa with very little pigment. The vessels in the papillæ are narrow and there is slight sclerosis of the vessels of the choroid. There is a postcortical cataract; marked limitation of visual fields. Vision: O. D., counts fingers at 15 cm.; O. S., counts fingers at 30 cm.

Teeth are partly defective; thyroid negative; mammæ very obese, nipples without pigment.

Genitalia: Labia majora flat, clitoris small, prepuce hardly apparent, the hymen fleshy. By rectal examination the vagina is found to be short, the uterus small and inclined backward, and the adnexa not palpable.

Roentgen-ray of the skull shows a moderate degree of brachycephaly, with occiput sheer. The sella turcica is small in width and configuration. The dorsum sella is plump and sheer.

Urine examination is negative; blood count is normal; Wassermann reaction negative.

There is mental torpor and a phlegmatic lack of interest. Menses occurred after administration of ovarian substance and then continued without further therapy. Sometimes they were substituted, and always accompanied, by nasal bleeding and headache.

The vision gradually improved under combined pituitary and thyroid therapy, and a gradual loss of weight amounting to 6 kg. occurred.

CASE II.—Ernest, aged sixteen years, weighs 54 kg. and measures 141 cm. in height. He has been fat since childhood, and has had defective sight. He is brachycephalic and his occiput is sheer. His hair is dense and coarse; cheeks are red; palpebral fissures narrow; nose short; eyebrows almost absent. He has very little hair on the body. His skin is dry, rough and cold, and over the thorax and extremities is mottled. There is marked adiposity, especially of the mammæ; and the lower extremities are fatter

than his sister's. The legs are column-like, the hands short and the joints broad; the fingers are thick at the base, the tips pointed. There is a sixth finger on both hands. There is slight genuvalgum. The feet are short and broad, and there are six toes on each foot.

Eyes: Pupils react to light and accommodation; there is an *atypical retinitis pigmentosa*. The vessels are broad, and there is abundant pigment; there is postcortical cataract, marked limitation of visual fields; marked diminution of vision. The oral opening is narrow, the teeth good; the thyroid is normal; thorax is short and barrel-shaped; heart and lungs are normal; the mammae are fatty, the nipples free of pigment. The abdomen is negative.

Genitalia: Scanty hair; there is a cushion-like, overhanging mons veneris and a nipple-like penis; the scrotum is divided into halves by a deep raphé; the testes are the size of beans; the prostate is not palpable.

Roentgen-ray of the skull shows moderate brachycephaly, a sheer occiput, and no evidence of increased intracranial pressure. The sella turcica is of normal width and configuration; the dorsum sellæ is plump and sheer.

Urine and blood examinations are negative; Wassermann reaction is negative.

Mentally the boy is childish and apathetic.

A third case, occurring in another family was likewise reported by Biedl:

A boy, aged thirteen years, showed adiposity (weight 66 kg.) and retinitis pigmentosa. The family history was negative.

Roentgen-ray of the skull showed a thick and plump dorsum sellæ.

SUMMARY OF BIEDL'S CASES. A brother and sister, of a family of 6 living boys and girls of healthy parents, showed atypical retinitis pigmentosa, adiposity, genital dystrophy, polydactylism and mental deficiency. Two others of the family who died in infancy showed polydactylism. (Assuming that these might have developed the full syndrome had they lived, we have the remarkable parallel of 4 healthy and 4 affected children in this group, as in Laurence's and in ours.)

Roentgen-ray of the skulls of the abnormal children showed no definite lesion of the sella turcica, but the dorsum sellæ were plump and sheer. The same was true of a third case occurring in another family. The brother and sister appeared to respond to hormone therapy.

Biedl regards the condition as a distinct syndrome.

Raab's paper, entitled "A Clinical and Roentgenologic Study of Hypophyseal and Cerebral Obesity and Genital Atrophy,"³ deals with this particular syndrome (of which he states there are

seven certain cases*) only as a part of a larger consideration of dystrophia adiposogenitalis. This he believes is not an unvarying condition, but has as its chief components obesity and genital atrophy or genital hypoplasia. His views, based upon the teaching of Biedl,† may thus be summarized:

In studying the genesis of dystrophia adiposogenitalis it is necessary to take into account the function of the hypophysis. Under normal circumstances the pars intermedia furnishes a secretion which is led off by the posterior lobe and stalk to energize certain metabolic and genitotrophic centers lying at the floor of the mid-brain (hypothalamic centers). If by reason of some abnormality, developmental or acquired, this secretion fails (a) to reach, or (b) to energize these centers, some form of dystrophia adiposogenitalis or of cerebral adiposity will result. There are thus three classes of disorder, according as (a) there is disease or defect of the hypophysis (pars intermedia), (b) obstruction of the pathway and (c) disease or defect of the cerebral centers. For example, tumors within the hypophysis causing injury to the middle and posterior lobes may give rise to the clinical picture from failure of secretion; as may tumors without, from obstruction of the pathway. Internal hydrocephalus may cause the syndrome by pressure on the hypophysis or by obstruction of the pathway, or by direct injury to the basal centers. Lesions or defects of the trophic centers themselves may bring about the symptoms, independently of hypophyseal failure, direct (structural or functional) or indirect (obstruction). Among such cerebral lesions could be: Encephalitic foci, tumors, tuberculosis or syphilis of the base of the brain, traumatism; the defects might be functional failures from acquired disease or disorder, or congenital abnormalities.

The *hereditary* (familial) occurrence of the syndrome may be occasioned by congenital hypoplasia of the hypophysis, by internal hydrocephalus and by anomalies of the skull, such as an abnormally high or massive dorsum sellæ. It will be recalled that in the particular syndrome of which we speak, Biedl stressed the importance of the last factor, that is, the high or massive dorsum sellæ, and Raab reëchoes the emphasis laid upon it as a mechanical element in this congenital form of cerebral obesity. He believes that the skeletal defects, polydactylism, and a high and perpendicular dorsum sellæ are similar anomalies, and that the sellar obstruction stands in direct causal relationship with the adiposity and genital dystrophy. Thus the thicker and more perpendicular the dorsum, and the more extended its contact with the third ventricle, the more

* He does not know of de Schweinitz's cases, of Engelbach's cases, of Laurence and Moon's cases, or of our cases. This brings the record, so far as known to us, up to 20 in all.

† No attempt has been made to preserve in this summary either the author's language or his method of statement.

likely is the syndrome to develop. He believes that pressure occurs at the edge of the dorsum, thus shutting off from the basal centers the energizing secretion of the middle lobe of the hypophysis.

G. E. de Schweinitz, in his *Bowman Lecture*,⁴ speaks briefly of the association of pigmentary degeneration of the retina with pituitary diseases and polydactylism. After citing a case of Bardet's published in a thesis of 1920 (and which is abstracted and included by Raab in cases from literature) he mentions 3 cases of this character that he himself, has seen. One responded well to organotherapy—vision, general condition and mentality showed distinct improvement; in another the effect seemed favorable, but not so pronounced. He suggests that subjects of pigmentary degeneration of the retina who are benefited by the administration of pituitary and thyroid extracts may owe their improvement to the corrective influence of these preparations upon an associated pituitary-body disorder.

Discussion. That the retinal phenomena of the syndrome described by Laurence and subsequent writers and which the cases here reported well illustrate, represent merely one phase of a general developmental failure, seems self-evident, and we need not stress the point further. Retinitis pigmentosa—to use the common term—has a very definite hereditary transmission, is often accompanied by nystagmus, strabismus, deafness, hare-lip, supernumerary toes and fingers and other anomalies; but its particular association with this form of dystrophia adiposogenitalis stands out as a distinct syndrome.*

For the sake of discussion let us accept Biedl's thesis in regard to the cause of cerebral obesity. He contends, it will be recalled, that the secretion furnished by the pars intermedia of the pituitary gland is led off through the posterior lobe and stalk to energize the centers regulating metabolism and genital growth, which are situated at the floor of the midbrain. If (a) this secretion fails to reach the centers, or (b) if the centers themselves are defective or diseased, and fail to react normally to the secretion, dystrophia adiposogenitalis will result.

We are then left with several possibilities as to the cause and pathological mechanism of this particular syndrome, which is unquestionably of congenital origin. Among such possibilities are congenital hypoplasia of the hypophysis, a high dorsum sellae obstructing the pathway and congenital defects of the midbrain.

* Thus Stör (Klin. Monatsbl. Augenh., 1865, p. 23; cited Brit. Oph. Rev., 1866, 2, 203), reporting on a patient with hemeralopia, six digits to each extremity, and mental retardation, does not mention adiposity or defect of the genitals. Höring, (Klin. Monatsbl. f. Augenh., 1865, p. 236; cited Brit. Oph. Rev., 1866, 2, 408) who found 4 cases of retinitis pigmentosa among 31 defective children in the institution at Stettin, whom he examined with special reference to this affection, mentions an associated feeble-mindedness. According to Nettleship (Trans. Oph. Soc. United Kingdom, 1909, 29, 37), progressive nerve deafness and idiocy seem capable of acting as mutual equivalents or substitutes in hereditary transmission of the complex associated with retinitis pigmentosa.

Engelbach,* who has seen, but not reported, two cases of this syndrome, has been rather in favor of the pituitary origin of so-called cerebral obesities in general; but perhaps the strongest point against direct pituitary genesis of the syndrome presented in our cases is the normal osseous development, the significance of which Engelbach† himself has specially emphasized.

Our own first tendency in regard to our patients was, indeed, to imagine, in spite of the inconclusive roentgen-ray studies, a congenitally deficient hypophysis. Reflection, while leading us to admit the weight of evidence against this view and in favor of congenital defect of the trophic centers, inclines us, nevertheless, to keep our minds entirely open and await the progress of research. The hypothesis advanced by Biedl and elaborated by Raab is more than highly plausible—it is seductive. But as yet there is no proof from necropsy that in cases like those here reported the hypophysis is not involved in the general imperfection of development. Hence, while we wish to go on record as to the distinctiveness of the syndrome as a pathological entity and the strong possibility of its cerebral origin, we are content to leave the question of the exact mechanism to further study.

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BELL'S PALSY; FOUR CASES OF INFECTIOUS ORIGIN.*

By VIRGINIUS DABNEY, M.D., F.A.C.S.,

PROFESSOR OF LARYNGOLOGY, RHINOLOGY AND OTOTOLOGY, GEORGE WASHINGTON UNIVERSITY, WASHINGTON, D. C.

In the year 1823, Charles Bell, an Englishman of keen powers of observation, noticed that in cases of facial paralysis, whenever the patient tried to close the eyelid of the affected side, the eyeball would roll upward and, upon persistent effort, outward as well. Facial palsy, as it was then called, of unknown, or at least proble-

* Personal communication to one of us (S. S.-C.).

† In a recent communication Engelbach and McMahon⁵ suggested, after a comparative study by roentgen-ray of the development of the bones in normal persons and in those subject to endocrine disorders, that the information thus gained may be of more value in diagnosis than basal metabolism, blood chemistry and other so-called specific and laboratory determinations.

* Read before the Academy of Ophthalmology and Otolaryngology, September 16, 1924.

matie origin, characterized by this sign came to be called "Bell's Palsy." The French observers in particular were struck by this symptom and due to Bell's persistence and apparent originality of perception consistently refer to it as "the sign" or "phenomenon of Charles Bell." From the very beginning cold was thought to be the cause of this paralysis of the brow, cheek, lip, eyelid, and, when involving that portion of the nerve lying within the Fallopian canal, taste and hearing as well. It is interesting in passing to recall the number and variety of diseases in which chilling of the surface of the body has been from antiquity regarded as causative of disease, whether it be pneumonia or chilblains, acute nephritis or eoryza, diarrhea or lumbago. The prevalence of the infectious diseases during cold weather seems to those ignorant of disease processes (not all of them laymen, at that) further proof of this belief, wherein they fail to realize that warm weather brings with it the open window and door, the admission of fresh air and sunlight to which no germ is long resistant.

In the year 1889, both Charcot, the neurologist, and Neumann, the otologist, spoke disparagingly of cold as a cause of facial palsy, and both seemed to feel that an inherited susceptibility to nervous disease was responsible for the paralysis. In support of his belief Neumann gave a history of one family in which three members were afflicted with this disorder. Bell was able to produce experimentally all the classical symptoms by severance of the facial nerve, but, as in the beginning of his observations, he concerned himself chiefly with the eye phenomena. He regarded the rolling upward and outward of the eye as "physiologie," due to the exaggerated effort to bring into play the now paralyzed orbicularis palpebrarum.

It is perhaps almost essential to a proper understanding of the different phases of this paralysis that the course of the nerve involved be clearly kept in mind. The most convenient and logical division for this purpose would seem to be into three sets of branches: (1) Those given off within the Fallopian canal; (2) those extracranial and given off before the terminal division; (3) the temperofacial and cervicofacial divisions. This threefold division is not merely an anatomic nicety, but will explain why some cases of Bell's paralysis show ear symptoms like tinnitus and slight deafness, indicating involvement of the chorda tympani and stapedius, while others are complicated by perversion of taste and impaired motility of the tongue, showing implication of the chorda tympani and glossopharyngeal. Again, there may be nothing but uncomplicated facial paralysis, where the inflammation attacks the nerve after its exit from the stylomastoid foramen.

Careful studies of many temporal bones seem to justify the conclusion that the right stylomastoid foramen is generally more constricted than the left and that this difference is found more often in the female. Thus, these two facts are sometimes regarded as

predisposing causes of Bell's palsy, inasmuch as women are certainly more often afflicted than men, and a narrow canal exit would give a pressure paralysis in the presence of an effusion. Again, clinically, this theory seems to be borne out by experience, as right-sided affections are more often seen in this disease. It is my firm conviction that every case of Bell's paralysis will be found to be of toxic origin, if care is exercised in the search for such a cause. It bears, in several respects, a very striking resemblance to herpes zoster, not the least of which is the cause: infection. I have not seen this comparison drawn by any writer though it is so suggestive that someone must have noticed it long before my time. Herpes was long supposed to be due to exposure to cold and to many other fantastic things, but we now know it to be result of infection of the ganglion. If exposure to a draft or cold wind causes facial paralysis, why doesn't it cause a simultaneous facial neuralgia, as the trifacial nerve is much more easily disturbed by such a cause and is much more vulnerable in the face and temple, by reason of the superficial nature of its distribution? Yet, it does not do so. With a heavy protective coat of bone, periosteum, muscle and skin, is it likely, or even possible, that cold would attack that part of the nerve lying within the Fallopian canal? Yet it would have to do so to cause taste and hearing perversions associated with facial palsy, since a neuritis of the nerve external to the stylomastoid foramen would not give any symptoms other than the paralysis. On the other hand, infection through the blood stream readily reaches any nerve anywhere, and the close confinement in a small, unyielding bony canal to which the facial nerve is subjected, renders a paralysis certain with the slightest effusion into the nerve sheath, such as is caused inevitably by an infection of that nerve. It is interesting to see that some of the older writers have shown sufficient courage and independence to consider "rheumatism" as a cause, and quite suggestive when we realize that cold was thought for many years as a cause, in turn, of this rheumatism. Thus, we gradually arrive at the real cause: infection, which is, of course, the cause of rheumatism. Thus, these gentlemen were not far away from discovering the real cause of facial palsy, though they were in blissful ignorance of their proximity. Of course, syphilis, tuberculosis, pressure by growths, parotitis, encephalitis and hysteria may severally cause a paralysis of the facial nerve, as well as the familiar otitis media in its various forms, but this is not the Bell's palsy of classical renown. Bell himself and his followers referred to a paralysis of unknown or problematic origin.

Most cases of this trouble show either tongue or ear symptoms, or both, associated with the facial distortion; in other words, the neuritis is intracranial, where, as I have pointed out, cold cannot strike, but where infection can easily do so. On the other hand, exposure to cold where a patient is overheated can readily be the

exciting cause of an acute exacerbation of a chronic trouble in the tonsils, teeth or nasal sinuses, and thus bring on a toxic neuritis of the facial nerve. In fact, I was able to demonstrate a definite causal relationship between each of these foci and a Bell's paralysis in the four cases which form the basis of this paper. Not only is this so in these cases, but I go so far as to say that I have never seen a case where I was not able to find an infectious cause. To me it seems the only reasonable explanation and cold at best merely a contributory factor. I have been particularly struck with the invariable presence of the nervous diathesis in every case that I have seen or have had under my own care, though I cannot make myself accept Chareot's belief that this is actually a cause. However, it is a most interesting phase of the disease and certainly exerts some influence on the prognosis and length of convalescence.

Case Reports. CASE I.—M., a highly nervous young man, much overworked, very conscientious in the discharge of his duties and hard pressed to support his family. Here is the clear-cut background of neurosis upon which Chareot lays with much justification such stress. In the course of my examination I observed that he had bitten his nails down deeply, which is merely another nervous sign. He had a complete paralysis, with all the tongue, facial and ear symptoms, of three days' duration when I first saw him. The onset was sudden, and attributed by him to exposure to a draft when he was overheated. He proved to have an acute empyema of the left antrum and acute exacerbation of a chronic tonsillitis. Irrigation of the antrum and swabbing of the tonsils with silver nitrate resulted in marked amelioration of all the paralytic symptoms in thirty-six hours and complete disappearance of all of them in ten days. The antrum was certainly the source of the infection, as his tonsils were not removed and his paralysis disappeared. However, a tonsillectomy should be done, of course, to prevent possible reinfection, and he was so advised.

CASE II.—In B., the nervous element was not prominent but was certainly present. He was a government clerk whose trouble had been well established for four days before I saw him. The mouth and cheek on the affected side were immobile, but the eyelids merely slow in closing, and the tongue only partially affected, there being some difficulty in keeping food out of the hollow of the cheek. The ear was not involved. He had had another attack five years before and attributed both attacks to exposure to cold wind while driving a car. He had buried tonsils with surface plaques of caseous material and palpable glands at the angle of both jaws. I removed his tonsils under novocaine-adrenalin infiltration and in two days the eye was closed easily and normally and in two weeks there were no signs of any paralysis.

CASE III.—G. This man had had his second attack in six months when I saw him, in consultation, and gave as the cause sitting on the ground when overheated from playing golf. I was naturally skeptical, holding the views of etiology that I did, but especially so as the day referred to was very hot and even the ground seemed warm. At this time the cause seemed to me to be the tonsils. His paralysis was absolute, such as is seen only in severance of the nerve, with epiphora and all the other distressing symptoms. The time-honored treatment of strychnin, hot and cold applications and faradism were all tried, and in two months most of the trouble was gone, though it was three months in all before the condition approached normal. Even then the eyelids looked sluggish. I was suspicious of his teeth, but contented myself with a recommendation of tonsillectomy. I lost sight of the case, not being mine, for a year, at which time he had his tonsils removed not for the relief of the paralysis but merely because he felt that his throat was uncomfortable in winter. Three months later a twitching of the mouth and eyelids, difficulty in closure of the eye and inability to whistle made him and his numerous advisors feel that my theory of infection was wrong as the tonsils had been out three months. However, it in no wise vitiated my theory, as I pointed out an upper bicuspid whose removal showed a large apical abscess and resulted in an apparently permanent cure of the paralytic signs. He still has some teeth that I think unsafe and that may cause a recurrence. While outwardly not nervous in the laymen's view of the word, yet this patient is one of the repressed, nervous types whose highly organized nervous system is subject to an exaggeration of subjective symptoms.

CASE IV.—P. This case was seen by me after a week's duration of the paralysis and was most distressing to witness, as she was a pretty woman, very sensitive because of her disfigurement. She had had neurasthenia six months before. The eye signs were most pronounced, chiefly because she had little play of expression and the lips were not so apparent in their sluggish movement. However, her tongue gave her the most trouble as she often bit it while eating and food accumulated in the cheek. She thought her trouble was due to washing her hair and allowing a draft of air to strike her head while wet. There appeared nothing wrong with the nose or throat unless it was a slight redness of both tonsillar pillars, and the small tonsils themselves were free of exudate, but, noticing a slight swelling over an upper molar I elicited the fact that she had had tooth-ache for ten days. A roentgen-ray picture showing some trouble at the root of that tooth, I urged immediate extraction which was followed in two days by relief of the eye symptoms, and in ten days of the whole paralysis.

Conclusion. To the objection that the disappearance of the facial paralysis and the removal of a focus of infection may be merely

a coincidence, and that cases recover without any surgical intervention, the reply is that this disease is singularly intractable under old methods of treatment and singularly amenable to treatment by removal of infection. Under non-surgical treatment requiring from one to six months for either cure or even lessening of the symptoms, and under surgical measures showing improvement frequently in two days and always in seven, with definite cure in twelve to eighteen days, depending upon the duration of the disease before removal of a focus of infection was attempted.

It is here pertinent to state of those conditions in the eye-grounds showing exudate and effects of infection, 60 per cent are due to apical tooth abscesses, 25 per cent to diseased tonsils, about 10 per cent to nasal sinus disease, and the remaining 5 per cent to infection elsewhere in the body, divided among foci in the gall-bladder, genito-urinary tract and the intestinal tract.

So far as clinical evidence can be conclusive, two facts stand out clearly in these cases and in all I ever have seen: (1) The definite connection, or at least presence of infection in cases of Bell's paralysis; (2) the existence of the nervous diathesis. I believe that every case will show some focus of infection, whether it be in teeth, tonsils, nasal accessory sinus or some other place and that such infection is the true cause of every case of what we have recognized since the time of Charles Bell as "Bell's Palsy."

AUTOMATIC SYNCHRONIZATION OF ROENTGEN-RAY EXPOSURES.*

BY F. MAURICE MCPHEDRAN, B.A., M.B. (TOR.),

AND

CHARLES N. WEYL, B.S.

(From the Henry Phipps Institute of the University of Pennsylvania and the Moore School of Electrical Engineering of the University of Pennsylvania.)

Theoretical Considerations. Three organ systems, the digestive, circulatory and respiratory, increase the difficulties of securing satisfactory roentgen-ray records because of their physiological movements. Gastrointestinal peristalsis is subject to varied rhythm and intervals, but the movements are slow enough to be followed by the eye and the desired phase recorded by moderately rapid exposure. The two remaining systems constitute interdependent but dissimilar problems. Their interdependence is due to enclosure of lungs, heart and great vessels in one cavity and the

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consequent influence of the activity and condition of each one on all the others. Their dissimilarity is due to their disparity in rhythm and in density, the heart and aorta requiring records with well-defined outlines, the lungs with contrast and detail. The respiratory rhythm is relatively slow, and arrest can be secured, usually in moderate inspiration, for the time of exposure, except in the very young and in cases of severe dyspnea. But the degree of chest expansion varies the tension, and therefore the compressibility and rebound, not only of the lungs, but also of the majority, at least, of the intrathoracic vessels. With the descent of the diaphragm and attached pericardium, the arch of the aorta and the lung root descend, and the thrust of the systolic discharge on the tracheobronchial bifurcation, and especially the left hilum, is increased. Thus, insofar as inspiration increases the tension of vessels about the lung root and throughout the lung substance, it is unfavorable to stillness and to satisfactory roentgen-ray records.

Roentgen-ray films of excised lungs show the radiating trunks in beautiful detail; yet densities of pathological origin are readily distinguished, since the fine normal constituents appear as branching lines and not as a confused blur of uneven mottling, such as commonly results from attempts to secure fine detail in the living. While the intensity of the roentgen rays necessary to penetrate chest walls must always tend to wipe out lung detail in the living, this is somewhat paralleled by the effect of edema almost constantly present in the excised lung.

The most difficult problem has been to catch the lung at rest. In a study of childhood tuberculosis, being carried on in the Henry Phipps Institute, it has been desired to secure records showing the presence and number of primary or focal tuberculous lesions in the lung substance and at the hilum. Most striking evidence of the extent of movement both of the hilum and the lung substance is obtained in these cases from stereoscopic films made in the usual fashion, that is, without synchronism with diastole. Examining a series of such films, one finds commonly in one of the pair the shadow of a calcified lesion, it may be 0.5 to 1 cm. in diameter, sharply outlined, lying 2 to 4 cm. or more lateral to the cardiac or aortic outline; in the other film of the stereoscopic pair, this lesion may be more or less blurred or even quite indiscernible. In the latter case the trunk shadows of the surrounding lung-field are found to share the characters of the outline of the calcified lesion; and usually it may be seen that the cardiac or aortic outline is blurred as well.

Such a finding is frequent even with exposures of 0.05 second, (timing checked against the perforated lead top). Rapid exposure reveals pulmonary densities that are not demonstrable by slower exposures. But it does not appear that rapid exposure alone, with present equipment, will meet the needs. The pulse wave in the large vessels travels some 3.4 to 4 meters per second, and is more

rapid with branching and decreasing caliber;¹ while it appears that the rate of propagation of the pressure in the large vessels may change from 3.2 to 17.6 meters per second. (See Fig. 2 reproduced from Fig. 23, *The Circulation in Health and Disease* (Wiggers).

These enormous changes in pressure, and in the relation of pressure in different vessels, occur in 0.12 second in this record. Subsequently there is a fall of pressure in all vessels; but it is much more rapid in the pulmonary artery than in the aorta, (compare Figs. 1 and 2 (Figs. 22 and 23 of Wiggers' *The Circulation in Health and Disease*). Further disturbances of lung detail may be caused by the vibrations of the blood column following systolic ejection, (see *c'-c*, Fig. 1), the reflection of the pulse wave at branches, and the effect of varying pressures in the curved elastic arteries—an influence insufficiently weighed in the physiology and pathology, especially of tuberculosis, of so mobile, compressible and elastic an organ as the lung. It is possible that the early diastolic rush of blood from the large venous trunks to the auricle also causes vibration of the adjacent lung in individuals with slowly beating hearts. Moreover, ventricular systole endures for 0.33 second, at pulse rates of 60, to 0.23 second at 120;² the volume of blood discharged being between 50 and 100 cc;³ and auricular systole, contributing 18 to 60 per cent of ventricular filling, (proportionately more the faster the heart beat), averages 0.11 second.⁴ The minimum of cardiac movement and of rate of change of pressures both absolutely in each vessel and relatively, as between pulmonary and systemic circulation, occurs in late diastole, and this period is therefore the best suited to accurate recording of pulmonary densities, normal and pathological. This period is represented in Fig. 1 as the time between *h* on the right auricle curve and the second *a* on the pulmonary artery curve.

In a study of heart volume changes, Meek and Eyster⁵ added synchronism to speed of exposure. Their method was to catch the rhythm of the heart beat heard through a stethoscope and to expose

FIG. 1.—Pressure changes in the pulmonary artery (upper) and the right auricle (lower). *Upper record*: *a*, auricular wave; *b*, preliminary vibrations; *c-e*, sudden systolic ejection throwing the column of blood into vibration; *d*, systolic summit; *e-f*, incisura. *Lower record*: *a-c*, auricular systole; *c-d-e*, early systolic vibration; *f*, small notch at end of systole; *g*, early diastolic fall, opening of tricuspid; *h*, mid-diastolic wave, occasionally present.

FIG. 2.—Synchronous pressure curves from aorta near semilunar valves (lower) and innominate artery (upper), showing changes in contour of pressure curve in aorta and its immediate branches and variable rate of propagation at different pressure levels. *A-C*, auricular systole; *C-D*, preliminary vibration during isometric contraction; *D-E-F*, primary oscillation; *F-G*, systolic maximum ejection phase; *G-H*, reduced ejection; *I*, incisura; *K*, after vibrations becoming larger in innominate. Velocity of transmission at *D-D*, 3.2 meters per second; at *H-H*, 17.6 meters per second.

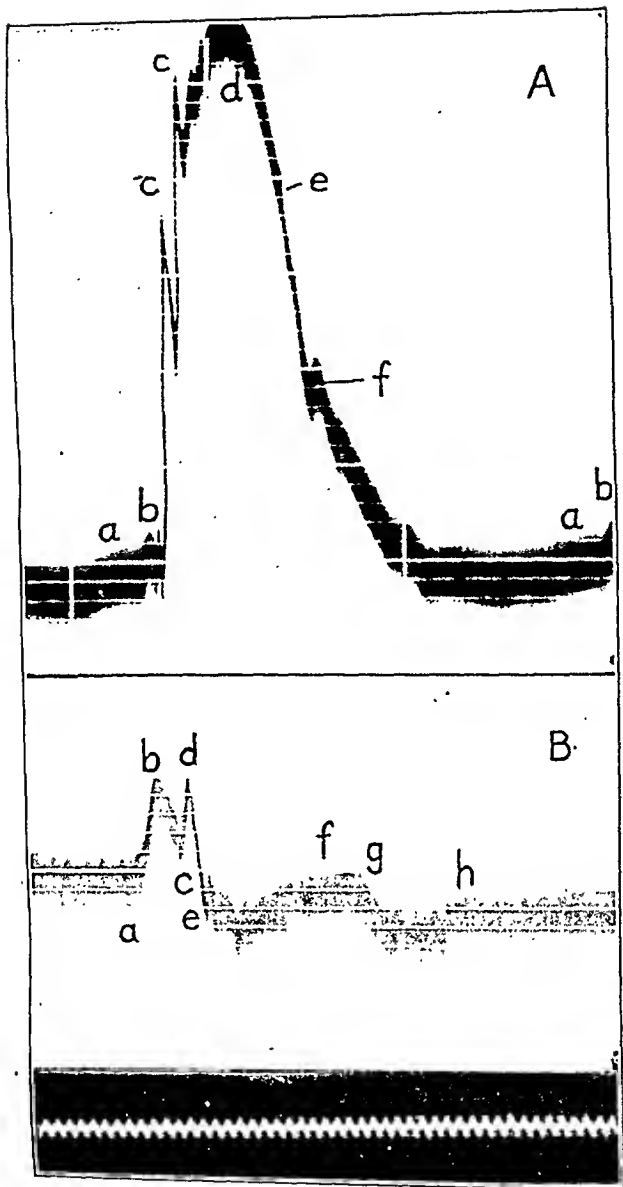
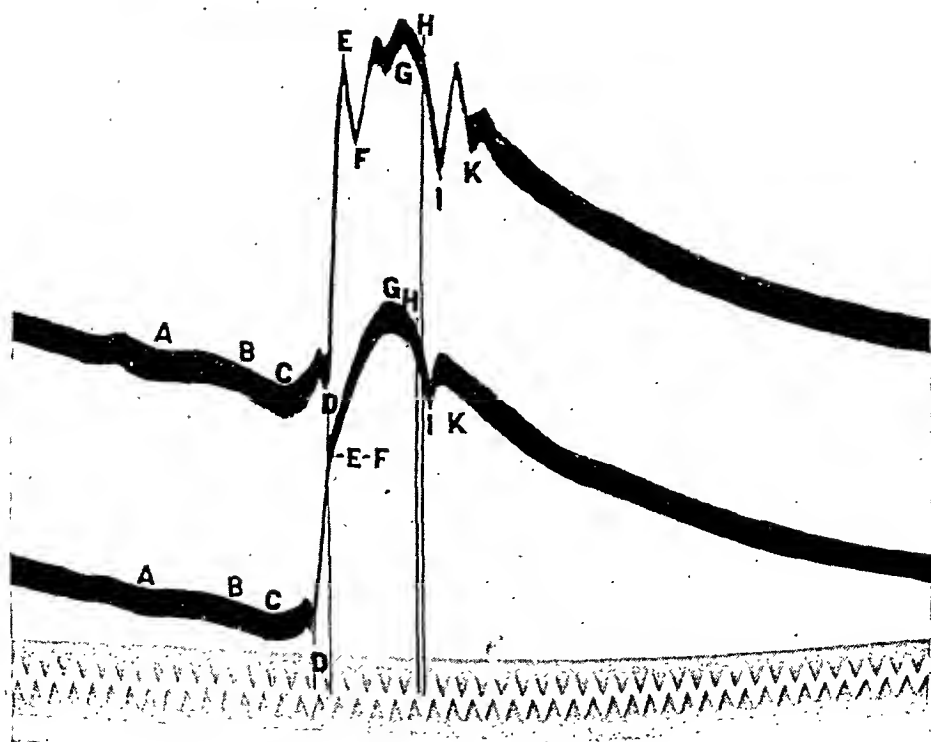


FIG. 1



Many methods were carefully investigated employing microphones with vacuum tube amplifiers, the electrocardiograph, the capillary electrometer, but were rejected because of failure to fulfill one or more of the requirements stated above.

The apparatus finally developed is very stable; results are readily and exactly reproducible; and the device is easy to apply.

Reference to Fig. 3 will make the principle of operation clear. Details are omitted in this diagram for the sake of clearness. *L* is a powerful light source, (stereopticon type of incandescent lamp). *C* is a pair of condensing lenses. *M* is a very small galvanometer mirror which is fastened to a flat phosphor-bronze galvanometer suspension ribbon, a horizontal section of which is shown at *U*. The torsion of this ribbon keeps the mirror *M* normally in the position shown in the diagram. *F* is an ordinary glass funnel which is connected to the tambour *T* by means of a flexible rubber tube. The tambour *T* is sealed with a diaphragm *D* of extremely thin

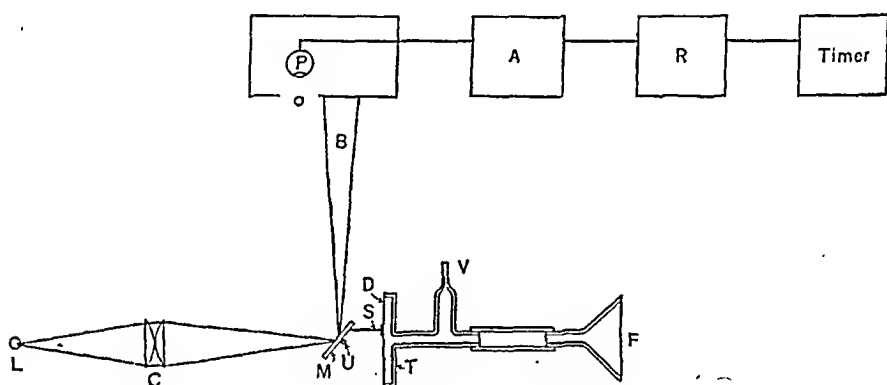


FIG. 3.—Schematic diagrams of apparatus for automatic synchronization.

rubber. By means of a specially constructed lever system, which, for simplicity is represented by *S* in the diagram, any motion of the diaphragm *D* is imparted, greatly amplified, to the mirror *M* which is then rotated about *U* against the restraining torsion of *U*. *P* is a photo-electric cell of the vacuum type, which is contained in a compartment having a light-admitting aperture at *O*. This photo-electric cell is connected electrically to the relay *R* through the vacuum tube amplifier *A*. The purpose of the relay *R* will be made clear later.

If the open end of the funnel be placed against the neck of the patient over the carotid artery, an impulse from this artery will travel through the rubber tube and displace the diaphragm *D*. This will in turn rotate the mirror *M* which deflects the beam of light *B* on to the photo-electric cell, causing a momentary current of extremely small magnitude to flow through the cell. This current which is amplified by means of the single vacuum tube amplifier

closes the relay *R*. This relay *R* closes 0.043 second after the pulse at *F*. This interval can be materially shortened by a somewhat more complicated apparatus. If no greater lag between the carotid pulse (or the apex thrust) and the exposure of the roentgen-ray film is desired, the relay *R* can actuate the roentgen-ray transformer primary directly. If, however, a greater time is desired, it is necessary to introduce a lag-timing device. For this purpose a standard roentgen-ray exposure timer was converted into a lag timer. Instead of having the timer determine the duration between beginning and end of exposure, it was adjusted to determine the duration between the closing of the relay *R* and the beginning of exposure. The length of exposure was controlled by a circuit-breaker.

Referring again to Fig. 3, *V* is an adjustable capillary vent for equalization of the pressure in the tambour, thereby assuring the return of the diaphragm *D* to the normal position after each pulse. The entire apparatus with exception of the funnel and attached rubber tube was enclosed in a light-tight cabinet so that no stray light should affect the photo-electric cell. The electrical connections and the mechanical details of adjustment have been omitted for the sake of clarity and brevity. A full description of the apparatus including constructional details will appear in the near future in an electrotechnical journal.

The Method of Use. There are subjoined (Fig. 4) photographic records of various lags or intervals between the carotid pulsation and the closing of the roentgen-ray primary. From the receiving tambour a rubber tube led to a *Y* tube, one arm connected to a Frank capsule carrying a mirror and set up before the camera: the other arm of the *Y* led to the tambour activating the photo-electric cell. The roentgen-ray exposure is shown as a faint band stretching across the paper, best seen on the white margins; the upper extremity delimited for clearness by ink. The carotid pulse tracing is represented by a dotted line, since an alternating current arc was used for the source of light. The tuning fork has a period of 100. The dark spot on 5 and 6 is due to roentgen ray penetrating the numbering aperture of the camera.

The work of Eyster and Meek has pointed out the value of synchronized roentgen-ray films to establish the volume changes of the normal heart. Only synchronized exposures give comparable records of heart outline to incorporate in clinical records. We are using this method also for study of the aortic arch and for lateral records of the tracheobronchial glands. Its usefulness for the lower half of the lung-field (for example, bronchiectasis) is greater than for the upper, partly because of cardiac movement and partly since the volume, and therefore the elasticity, is greater, and the vessels are longer.

Deductions drawn from the appearance of the hilum shadow are questionable unless the exposure is diastolic. Much of the "broad-

ening and thickening of the hilum" is artefact due to cardiac and aortic pulsation. And it appears probable that much of the "peritruncal thickening of ascending trunks" is also due to vibration. No instance occurs in a study of 318 excised lungs, and it has not appeared in satisfactorily synchronized exposures of the living.

It is just possible that synchronization may be helpful in gall bladder work since the aortic pulsation will be somewhat communicated through the air-containing viscera.

A subsequent article will deal with calibration.

We wish to express our indebtedness to Dean Harold Pender of the Moore School of Electrical Engineering for his interest and advice, and to Prof. H. C. Bazett of the Department of Physiology for suggestions as to timing and recording methods for calibration and for helpful references to the literature.

Summary. Roentgen-ray records of the heart and lungs lack in definition and in comparability, by reason of cardiovascular movement.

A mechanism is described by which exposures may be made at any selected phase of the cardiac cycle.

Systolic and diastolic cardiac outlines are reproducible at will.

Pulmonary records can be made when cardiovascular movement is at the minimum.

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ELECTROCARDIOGRAPHIC STUDIES OF THE EFFECTS OF ETHER UPON THE LIVING CAT'S NORMAL HEART.*

BY H. R. MILLER, M.D., AND DAVID FELBERBAUM, M.D.,

WITH THE ASSISTANCE OF

H. T. KRIGEL, PH.D.,

NEW YORK.

(From the Medical Service of the Montefiore Hospital, New York City, Dr. B. S. Oppenheimer, Chief of the Medical Division.)

OUR interest was directed to the influence of ether upon the living cat's heart while investigating this organ electrocardio-

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graphically for the effects of ouabain in etherized cats. Cardiac irregularities were encountered, and an attempt was made to determine whether these derangements were caused by ouabain alone, by ether alone, or by a summated result of both drugs. Obviously, therefore, it was important to establish what the electrocardiograms of a normal cat's heart would be, the animal receiving no drug.

To this end a simple box was devised, into which a cat could be placed. The limbs, though fixed by strings, were readily accessible, the neck was firmly held and the animal kept in one posture by tying down the movable lid of the box at an adjustable angle. In this box the animal would remain quiet and undisturbed while the electrocardiograms were taken. The limbs of the animal were carefully shaved and wrapped with 3-inch wide flannel bandages, soaked in hot hypertonic salt solution. The bandages were led off from the wrapped-up shaved areas of the limbs to basins containing hot hypertonic salt solution and saline-filled porous jars; the bandages were partly immersed in the jars and the basins. Adequate protection was secured by rubber sheeting wrapped about the flannel-banded limbs, thus keeping the bandages warm, preventing dripping and short-circuiting. Before proceeding with the actual experiments the three leads were taken in the usual fashion. In all instances they were standardized, so that 1 cm. deflection equalled 1 millivolt of current. The galvanometer used was the large-size Williams-Hindle apparatus, the string's resistance being 6400 ohms. In a few experiments the Cambridge outfit was employed in a similar fashion. The standardization was maintained at 1 cm. for each millivolt of current, except in rare instance where time was pressing because of the precarious condition of the animal. Whenever normal standardization was not possible this condition was indicated at the beginning of each record. After taking the normal records the protocols of each experiment were carried out. Lead II was the usual derivation recorded unless otherwise stated.

In this manner 5 cats (Group A) were observed: Cats 105 (Ekg. 19), 113 (Ekg. 24), 116 (Ekg. 25), 117 (Ekg. 26) and 147 (Ekg. 50). As far as could be ascertained, these animals had never been employed previously in any experiments. Three additional cats, 130 (Ekg. 37), 131 (Ekg. 38), 145 (Ekg. 48/02), are placed in Group B. These animals had received ouabain in water or in oil, intramuscularly, but were not studied for any ether effects until several days (two days for Cats 130 and 131 and six days for Cat 145) had elapsed after the administration of the digitalis bodies, and until, clinically and electrocardiographically, no drug effects could be detected. An analysis of these records is given in Table I, and permits the following conclusions regarding the usual characteristics of the normal electrocardiograms of the cat:

TABLE I.—GROUPS A AND B.

Ekg. No.	Cat No.	Date, 1923.	Ld.	P.	R.	T.	Rt.	Electrocardiographic changes.	Remarks.
19 ..	105	Feb. 9	1 2 3	— + +	— + +	+ — —	250 230	Regular rhythm	Female; tightened on back to wooden board.
24	113	Feb. 14	1 2 3	0 + +	+ + +	— — —	270 270 270	Regular rhythm; no iso-electric period	Female; placed on abdomen in box.
25 ..	116	April 9	1 2 3	+ + +	+ + +	+ 0 0	..	Low voltage	Male; placed upon abdomen in box.
26 ..	117	April 9	1 2 3	± + +	+ + +	0 — —	210 200 200	In Lead I doubtful ventric. extrasystole; no special significance; probably due to muscular movements	Same cat had been used for Ekgs. 26 and 38; after 26 it received ouabain; it was used again without ouabain for Ekg. 38; female; placed upon abdomen in box.
38	131	April 18	1 2 3	0 + +	± + +	0 — —	280 280 270	Regular rhythm	
50	147	May 10	1 2 3	0 + +	— + +	+ + +	200 200 200	Regular rhythm	Female; placed on abdomen in box.
37 ..	130	April 18	1 2 3	0 + +	— + +	± + —	270 230 240	Female; placed on abdomen in box.
48 (1)	145	May 3	1 2 3	+ + +	— + +	+ + +	170 170 170	Male; placed on abdomen in box.
48 (2)	145	May 3	Was taken 5 min. after 48 (1), with same result	

Ld., lead; +, upward; —, downward large; 0, zero.

(Group A consists of 5 animals never used before experimentally. Group B consists of 3 animals used for ouabain experiments, but rested a sufficiently long time for effects of the drug to disappear. In none of these 8 cats was a drug given during the taking of the electrocardiograms.)

1. In Lead I there is no constant form or direction of the *P* wave or of the main ventricular deflection. The *T* wave could rarely be identified. The electrocardiographical picture varied in almost every animal. This lead, therefore, cannot be used in evaluating a standard electrocardiogram for the normal cat's heart.

2. In Leads II and III the *P* and *R* waves were upright. The *T* wave was downwardly directed or negative in 62.5 per cent of the cats examined.

3. The heart-rate ranged, as a rule, from 200 to 270 (mostly 200). It was 170 in Cat 145 (Ekg. 48). In a number of the cats

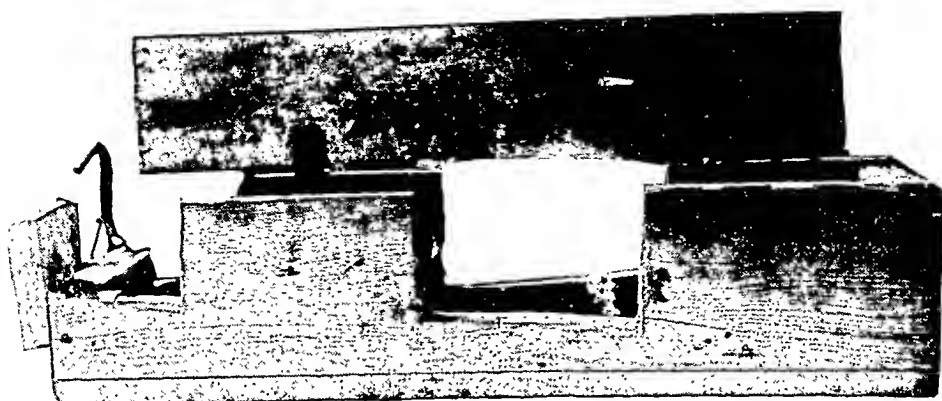


FIG. 1

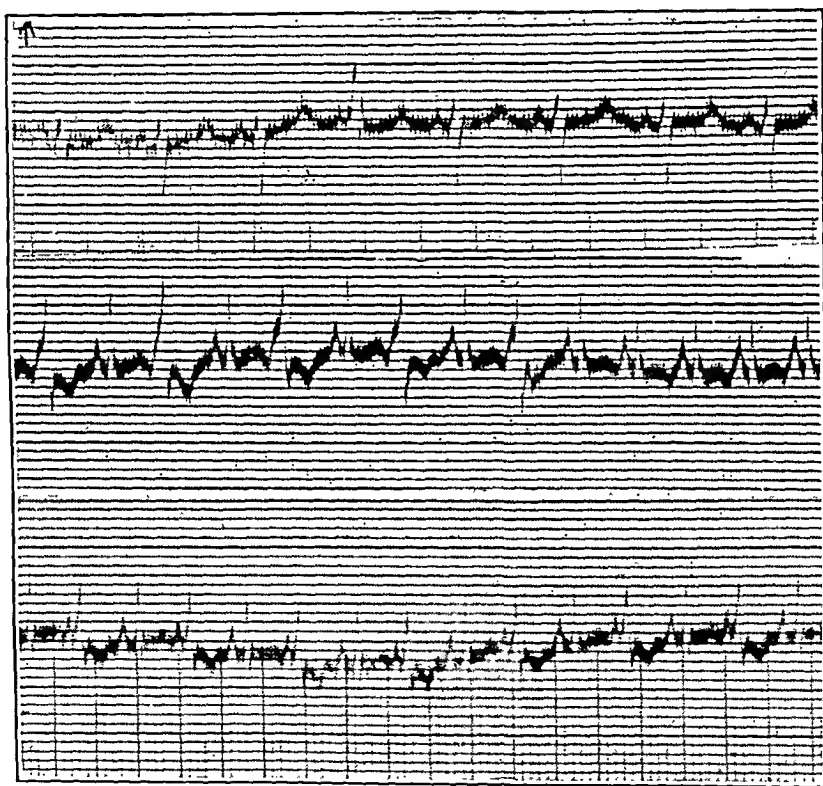


FIG. 2.—Ventricular extrasystoles. Ekg. No. 50 of Cat 147. The first record shows a single extrasystole. The second record shows in its first part extrasystoles alternating with normal beats; the later portion shows again an occasional extrasystole. In the third record a return of the alternating extrasystole takes place upon renarcosis of the animal. Chart II presents the further details of this experiment.

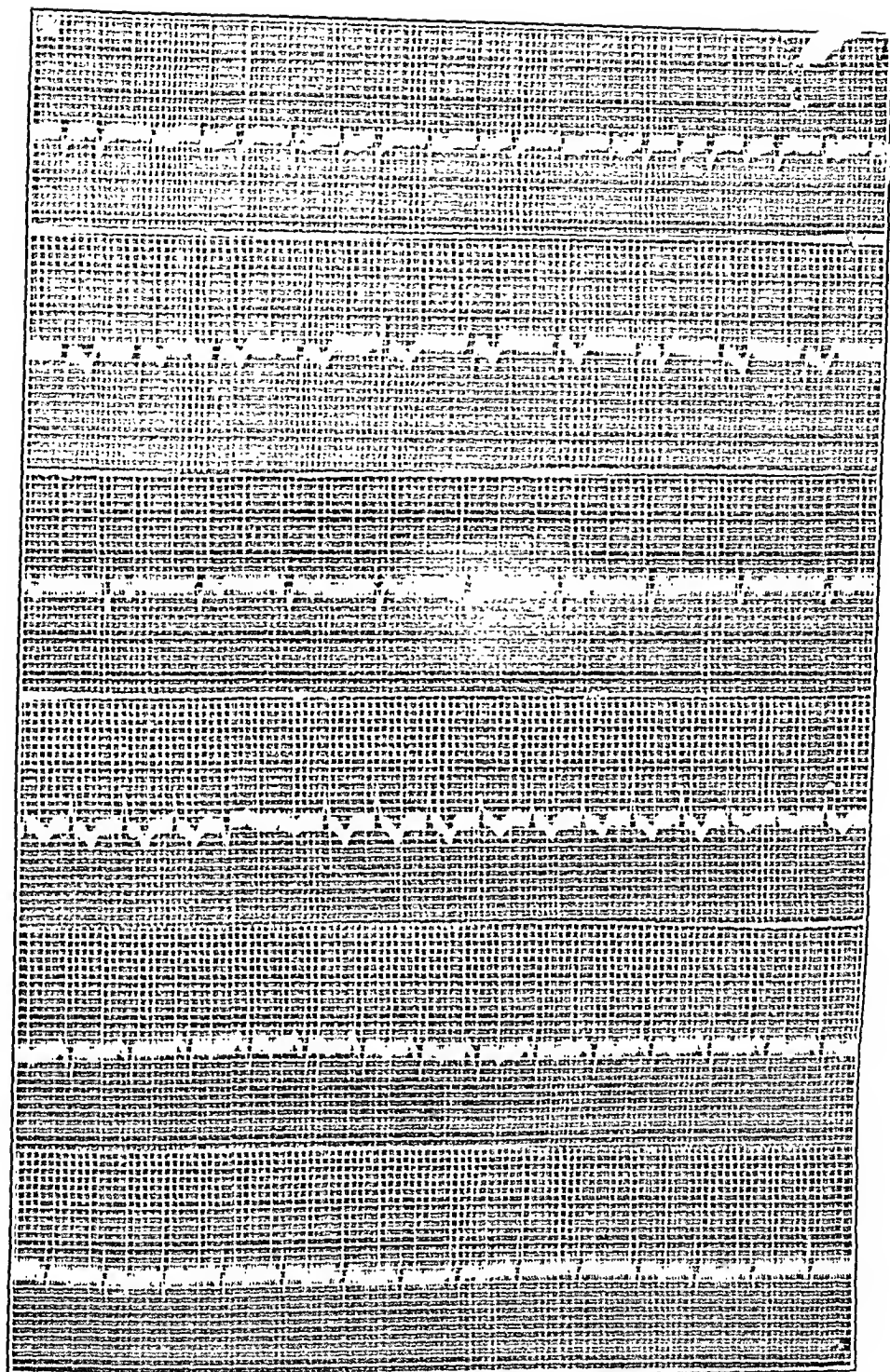


FIG. 3.—Ekg. No. 14 of Cat 100. The first record shows the irregularly acting heart with no evidences of auricular activity (auricular fibrillation). In the second record a high degree of conduction defect is seen in part of which the auricular complexes are submerged; slight evidences, however, can be made out in the deeply inverted *T* waves. There are also regularly recurring changes in the form of the *R-S* deflections. In the third record a 2-1 heart-block is evident, while in the fourth record a rapid nodal rhythm has developed with a curious alternation in the directions of the *T* and *R* waves. Finally, the normal mechanism reasserted itself, as seen in the last two records, upon recovery from anesthesia. Chart III is the protocol for this experiment.

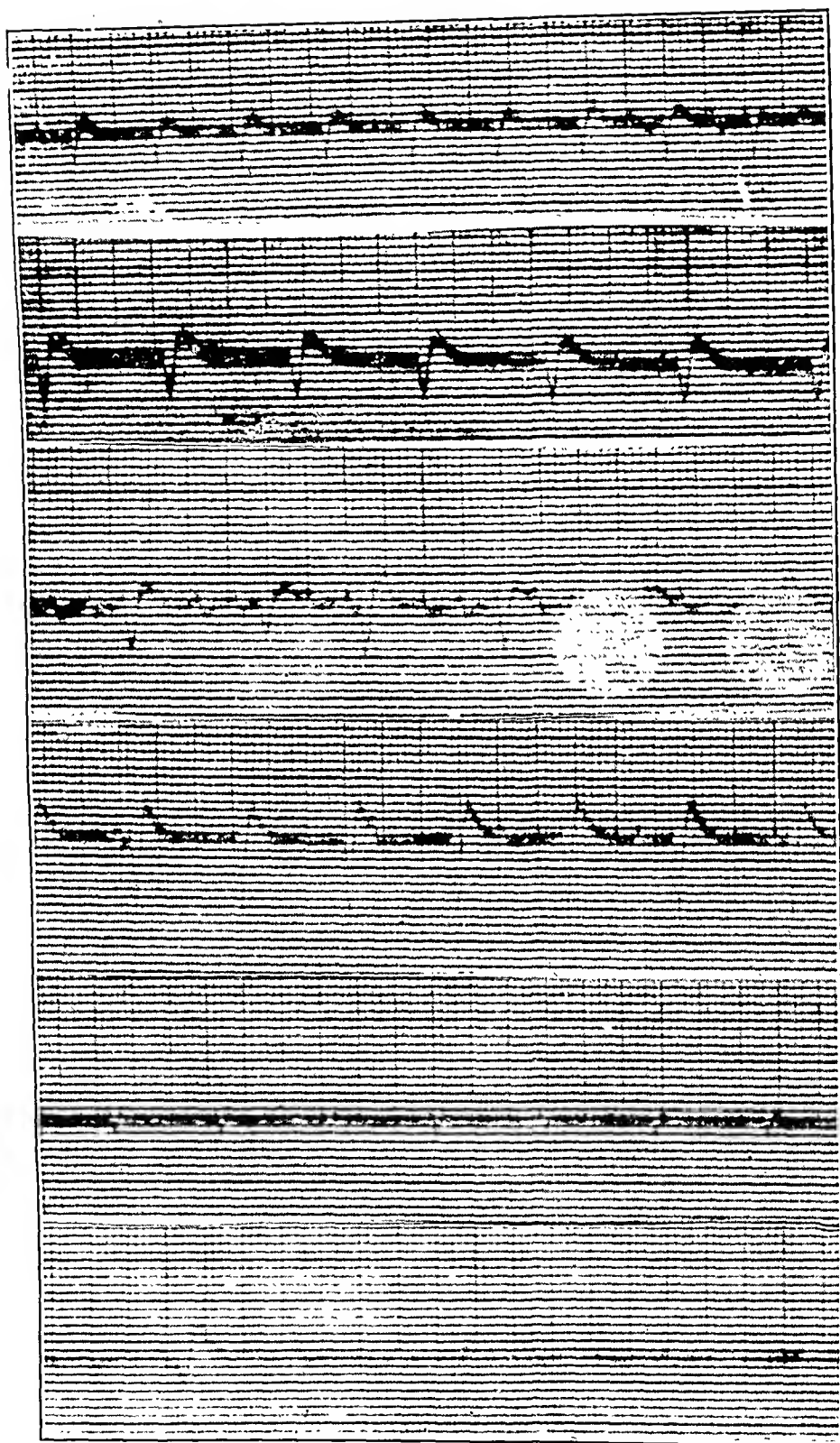


FIG. 4.—(See description on page 520.)

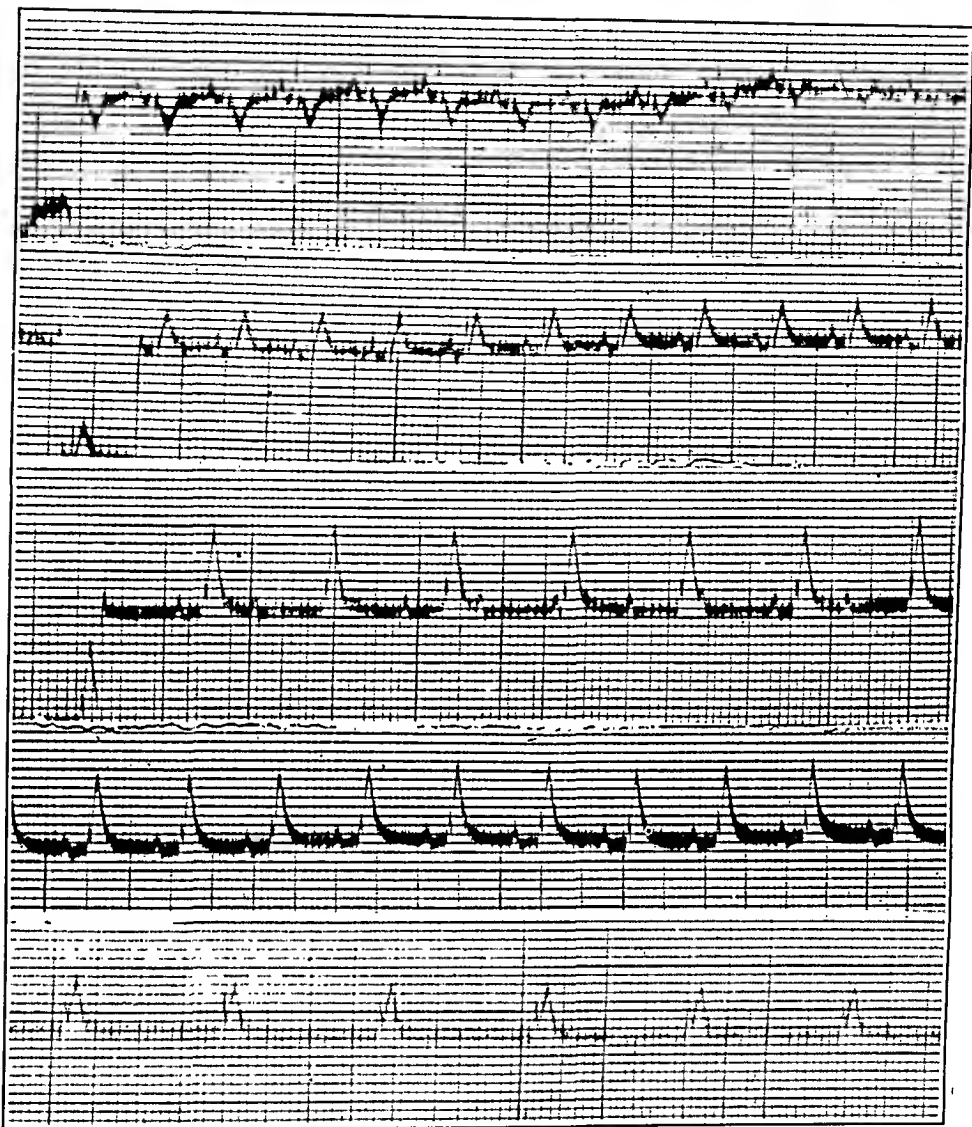


FIG. 5.—Ekg. No. 49 of Cat 146. This series of records shows a gradual change in the form of the *R-T* complex, the onset of a heart-block with a final idioventricular beat, and a complete absence of auricular activity. Record 1 exhibits the *T* wave gradually assuming an upright form from a deeply negative one. Record 2 is a continuation of 1, the *T* wave has now become part of the *R* and continues to rise until it is larger than *R*. Record 3, the *T* wave now overshadows *R* which appears as a notch on the up-stroke of the *T*. The *P-R* interval has progressively increased and in the fourth record a gradual onset of heart-block is seen with a slowing of the entire heart cycle. Record 5 exhibits an abnormally wide and notched ventricular complex; there are no evidences of auricular activity. See Chart V for protocols.

spontaneous variations in the rate of the heart-beat were noted during the periods of examinations.

4. The rhythm was regular in all these cats except in Cat 117 (Ekg. 26). This animal also had a wide *R* and a curious form in its *R-T* complexes, that is, the *T* wave joined the *R* wave before the base line was reached.

Discussion. We may, perhaps, assume when an apparently healthy normal cat is held securely in a simply contrived box, such as the one figured in the text, and when the animal has received no drug whatsoever, or even when a drug like ouabain is given, but sufficient time has been allowed for the drug to become eliminated, or for its effect to disappear, such an animal will exhibit in its electrocardiograms, when taken by the usual three leads, a regular cardiac rhythm, a heart-rate of approximately 200 beats per minute, with frequent inversion of the *T* wave in Leads II and III; and changes always in Lead I, of so diversified a character, as to permit of no constant interpretation. We have observed no "great frequency of spontaneous rhythm,* no spontaneous bigeminy." On the other hand, spontaneous changes in the rate are very frequent.

To properly determine any electrocardiographic effects upon an experimental animal such as the cat, an unanesthetized animal is preferable. Even small amounts of an anesthesia may add electrocardiographic changes that cannot be separated from those caused by a drug or any procedure under investigation. This point we shall try to demonstrate later in the text.

In a consideration of the probable influence of ether upon the living cat's normal heart, *in situ*, a prime difficulty lay in procuring an accurate means of giving ether in exact doses as an inhalant.

* S. A. Levine (Jour. Exper. Med., 1919, 29, 485) writes of the frequency of spontaneous nodal rhythm in the normal cat's heart. A perusal of the text of his carefully conducted work indicates that all cats used by him received ether narcosis in order to permit the undisturbed taking of electrocardiograms. In reply to an inquiry from us as to whether electrocardiograms were procured in normal cats uninfluenced by an experimental procedure whatsoever, Dr. Levin was good enough to write as follows: "Concerning the occurrence of nodal rhythm in cats, I remember distinctly that occasionally this was found even before any anesthesia was administered. Unfortunately, in the table I published in the article that you refer to, one could not be certain whether nodal rhythm developed before or during the anesthesia. I feel sure that it was not rare to find this arrhythmia in the first tracing taken before any drug at all was administered. I have since twice seen it occur spontaneously in cats. We had similar experiences studying the electrocardiographic tracings of patients during operation (Arch. Int. Med., 1922, 30, 57). I feel that it is a fairly common spontaneous arrhythmia both in normal people and in animals. Just yesterday I took a tracing of a normal dog as a control and happened to find nodal beats. This dog had received no anesthetic of any kind, either local or general." We wish to comment in this connection that in the study of a small group of cats unanesthetized and untouched by any drug, little or no change could be discerned in the electrocardiographic pictures of their hearts. In view of our experiments that increased amounts of ether can produce distinct and striking cardiac disturbances we hesitate to exclude the possibility that so-called spontaneous heart derangements may not be due to narcosis.

narcotic. It is well known that cats take ether easily, that anesthesia is obtained promptly, but that evenness in anesthesia calls for skill and constant vigilance. Not infrequently do cats suddenly die from seemingly small additional amounts of ether. We studied theoretically several means for administering ether in a quantitative way, but they seemed to be cumbersome and unsatisfactory. Eventually, therefore, we were compelled to resort to the crude drop-cone method as the only practical procedure. The respiratory excursions, the color of the mucous membranes and of the tongue, the amount of salivation, the status of the reflexes, especially the corneal and pharyngeal, these were our guides in estimating the depth of the anesthesia. For practical purposes they served fairly well.

The animals were enclosed in the box previously described or were attached to a board, allowed to grow quiet and relaxed, then anesthetized with ether. Ether was given in changing degrees of concentration and over varying intervals of time. In some experiments we tried to give continuously a so-called "light anesthesia," or "moderate anesthesia," or "deep anesthesia." These terms though loosely employed, signify in a measure a quantitative difference in the type of anesthesia obtained. Again, some cats were started with light anesthesia and the narcotic increased in crescendo fashion until profound anesthesia was obtained; sometimes death resulted. The reverse procedure was also carried out, that is, an initial deep anesthesia, gradually diminishing the amount of anesthesia until the cat recovered completely. Finally, some animals received alternating brief light anesthesia followed by quickly produced deep anesthesia, or *vice versa*.

Cats 99 (Ekg. 13), 100 (Ekg. 14) and 101 (Ekg. 15) were attached to a wooden board. Cats 145 (Ekg. 48), 146 (Ekg. 49) and 147 (Ekg. 50) were placed on their abdomen in the box. Cats 99, 146 and 147 were never used before; Cats 100, 101 and 145 were ouabainized in previous experiments. Charts I and II illustrate the effects

FIG. 4.—Ekg. No. 15 of Cat 101. These records show very remarkable and pronounced electrocardiogram changes induced by deep and fatal narcosis. The records were taken almost continuously. Record 1, only an occasional auricular complex is visible, the ventricles beating regularly at 105 beats per minute; the *T* wave rises directly from the stem of the *S* wave. Record 2, heart-rate is much slower, the auricles are at a standstill and the ventricular complexes are abnormally widened, and the *T* wave is blunt and directly continuous with the *S* wave. Record 3, a remarkable and abrupt change takes place; the auricular activity has returned but as an auricular flutter; the deflections are diphasic, 300 per minute and regularly recurring; some of these fall upon the *R* and *T* waves, distorting them; the ventricular complexes have not changed from that seen in Record 2, and are beating at 83 per minute. Record 4, the ventricular complexes are now of higher amplitude and still abnormal; there is a complete heart-block. Record 5, only auricular complexes are observed; the ventricles are now at a standstill. Record 6, only irregular, variable, small oscillations are visible, the origin of which it is not possible to determine. See Chart IV for protocols.

of varying amounts of ether anesthesia on the normal living cat's heart. The animals were narcotized fully, but only for a very brief period, and immediately allowed to come out of the anesthetic.

CHART I.—CAT 99. ELECTROCARDIOGRAM 13 (NOT PRINTED IN THIS ARTICLE). DECEMBER 23, 1922.

Record No.	Time, P.M.	Electrocardiographic changes.	Anesthesia.
0-1 . . .	3.50	Variations in height of <i>R</i> and <i>S</i> waves in all three leads, <i>S</i> predominating	Cat deeply under ether; at end of record out of anesthesia; eye reflexes active.
1-1 . . .	3.55	Variation in depth of <i>S</i> is marked, especially in Lead II	Deeply under; no eye reflexes.
1-2 . . .	4.03	Increase in rate; respiratory variations in <i>S</i> were less marked; <i>T</i> wave toward end of record became distinctly negative in Leads II and III	Deeply under.
1-3 . . .	4.07	Variation in depth of <i>S</i> wave marked; <i>T</i> wave again upright; <i>S</i> wave increased in size	Respirations regular and eye reflexes present; at end of record moving legs.
1-4 . . .	4.10	No change	As above.
1-5 . . .	4.13	Respiratory variations in <i>S</i> wave	Cat came out of anesthesia; reflexes all present.
1-6 . . .	4.16	Slight respiratory variations in <i>S</i> wave	Almost out of anesthesia.

Résumé. During the height of general anesthesia there were marked variations in the size of the *S* wave. These were distinctly of a respiratory type. Also changes in the direction of the *T* wave were noted, becoming negative but promptly recovering its upright direction with the cessation of the anesthesia.

The following charts, III, IV, V and VI, are protocols of Cats 100 (Ekg. 14), 145 (Ekg. 48) 146 (Ekg. 49) and 101 (Ekg. 15). The animals responded by cardiac disturbances of serious nature, varying in degree and type directly with the amount and duration of the ether narcotic administered. Some were anesthetized up to death and the progressive changes recorded continuously.

In these experimental records we see that during light anesthesia (analgesia) minor electrocardiographic changes, such as variations in voltage, sinus arrhythmia and changes in the direction of the *T* wave occur. An upright *T* is likely to become isoelectric or even negative, while the reverse is true of an originally negative *T* deflection. Inversion of an upright *T* is considered a very important evidence of digitalis effect. In view of the above experimental findings with etherized cats, for experiments with digitalis bodies employing such narcotized animals, this change in the *T* wave evidently should not be used to evaluate digitalis effects.

CHART II.—CAT 147. ELECTROCARDIOGRAM 50. MAY 10, 1922.

Record No.	Time, P.M.	Electrocardiographic changes.	Anesthesia.
0-1 . .	3.33	Normal Ekg. Lead I deflections are however poor and of very low voltage	At 3.31 light anesthesia for 2 min., then no anesthesia; eat out at 3.33.
0-2 . .	3.35	Same as 0-1	Anesthesia continued and then interrupted for 1 min.; eye reflexes present.
0-3	Same as 0-1	Moving limbs.
0-4	Sinus variation	As above.
0-5 . .	3.47	Variations in the height of R and sinus variations	Almost out of anesthesia.
0-6 . .	3.57	Cat's movements distort the electrocardiograms; T wave is now iso-electric	As above.
0-7 . .	4.05	Same as 0-6	Moving about actively.
0-8 . .	4.12	In groups of from two to twelve beats ventricular extrasystoles alternate with a normal beat	Anesthesia deepened; no anesthesia was given from 0-2 to 0-7.
0-9 . .	4.25	Sinus arrhythmia; T wave flat single extrasystole in Lead I	As above; 50 min. of light anesthesia (first stage).
1-1 . .	4.36	Normal ekgs.; T flat	Considerable salivation and eye reflexes present in 1-1;
1-2 . .	4.36	Normal ekgs.; T flat	no reflexes during 1-2 and 1-3.
1-3 . .	4.38	Normal ekgs.; T flat	Ether for 2 min.
	4.38 to 4.40	No records taken	
1-4 . .	4.40	Long-continued series of alternating extrasystoles, identically like those in 0-8; later record shows a normal mechanism, very rapid 250, with an inverted T; gradually this tachycardia slowed down to 187, and T wave became upright	Deeply under; no ocular reflexes.
	4.45	Pupils dilated; eat out of ether.

Résumé. A very remarkable repetition of the ventricular extrasystoles was produced during anesthesia, with changes in the T wave during the stage of deepening anesthesia and recovery therefrom.

During slightly deeper anesthesia, ventricular extrasystoles and varying degrees of depression of the conduction system were noted from a simple prolongation of the P-R interval to a complete heart-block and even standstill of the ventricles for long periods. Also high-grade toxic effects in the form of the ventricular deflections were repeatedly seen. It is not our purpose at present to attempt a discussion whether these changes are directly the result of the anesthetic or whether they may be in part explained by other factors, such as an increase in the carbon-dioxide concentration in the blood or an anoxemia as experimentally shown by Greene and

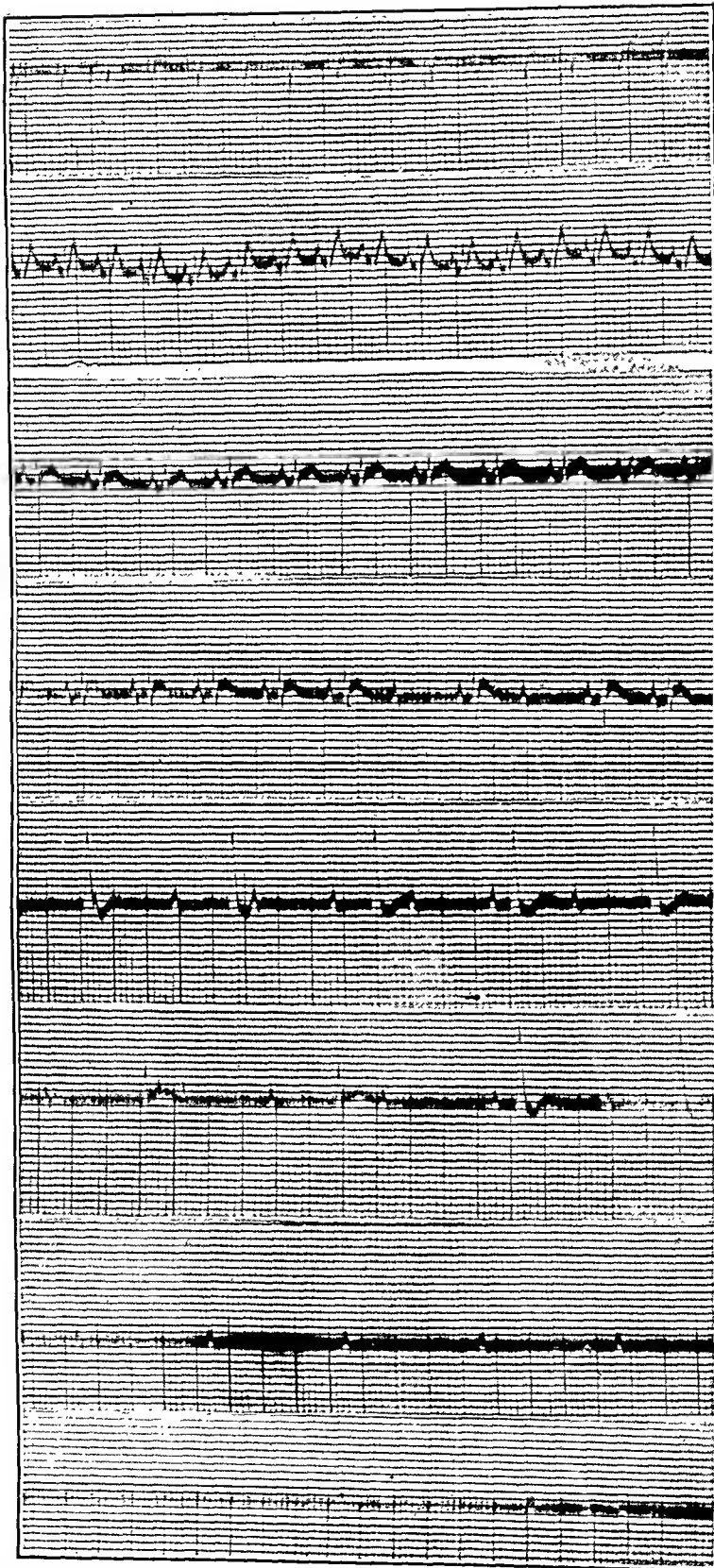
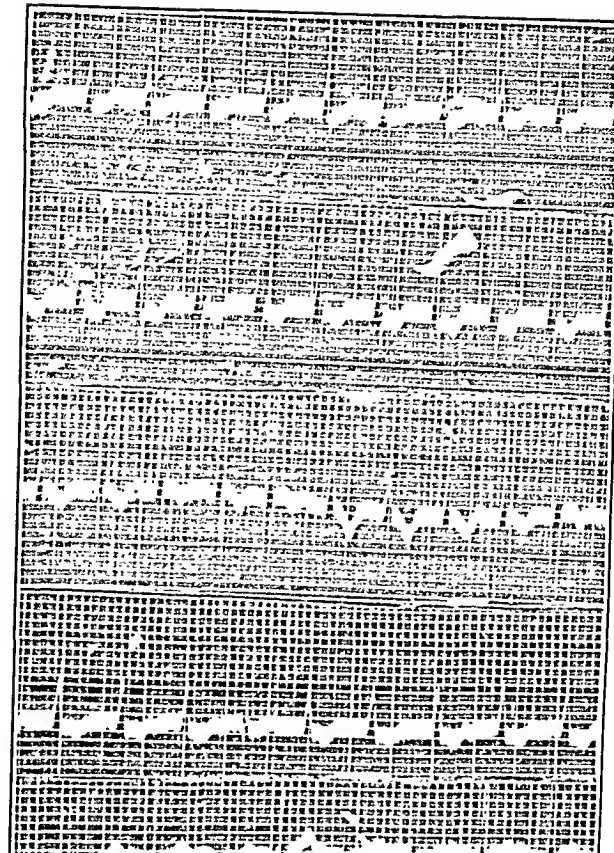
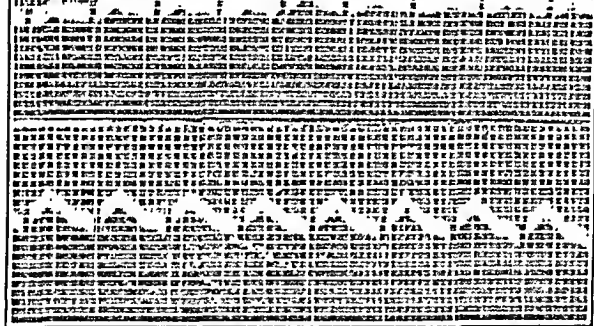


FIG. 6.—Ekg. No. 48 of Cat 145. These records exhibit a gradual slowing of the cardiac cycles with a progressive conduction disturbance until a heart-block is established in Record 4. In Record 5 the block has become complete with a slow auricular rate and an idioventricular beat of abnormal character, resembling that seen in bundle branch block. In the sixth record there is only an occasional idioventricular beat; the majority of the beats are of supraventricular origin, however. Finally, in Records 7 and 8 ventricles cease to beat and only a slow auricular response is seen. Protocol in Chart VI.

a



b



c

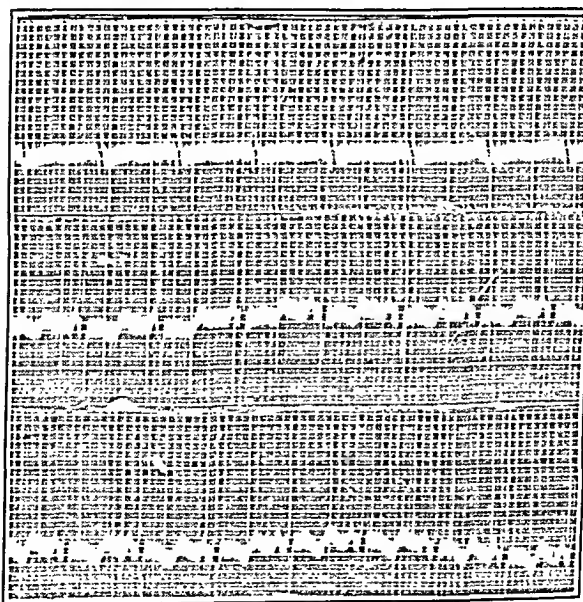


FIG. 7

CHART III.—CAT 100. ELECTROCARDIOGRAM 14 (SEE PRINTS).
DECEMBER 23, 1922.

Record No.	Time, P.M.	Remarks.	Anesthesia.
2-0 and 2-1 . .	4.20 4.31 to 4.33	No records taken Auricular fibrillation in Lead I; in Lead II a high-grade defect in the conduction system was seen; in the first 4 beats the <i>P</i> wave was apparently submerged, possible evidences being indicated by slight variations in the deeply negative <i>T</i> waves; the next 4 beats showed unmistakable conduction disturbance; gradually the <i>P-R</i> interval shortened and the <i>R-S</i> phase varied in a progressive manner; the next 5 beats repeated the condition of the first series exactly and then a second series was repeated; this alternation of event continued for a considerable time	Anesthesia begun. Anesthesia was deep; respiration stopped during Lead II and were very irregular in Lead III.
2-2 . .	4.35	A slow regular mechanism	Reflexes returned; cat licking its nose; no anesthesia.
2-3 . .	4.45	Partial heart-block 2 to 1	Again was brought deeply under anesthetics; respirations irregular, deep and slow; anesthesia discontinued.
2-4 . .	4.50	Regular normal mechanism returned; slow rate; all deflections increased in amplitude.	Cat out and moving about.

Résumé. This table demonstrates clearly the effects of deep anesthesia, the rapidity of onset of these effects, and the promptness of recovery. During deep anesthesia an auricular fibrillation occurred. In the stage of recovery from this anesthesia a curious series of events followed: First a high-grade depression of the conduction in the bundle of His developed, giving an interesting group of alternating electrocardiographic pictures due to the variations in the degree of this depression of conduction. Then the normal sino-auricular mechanism of the heart-beat returned, and the animal recovered from the anesthesia. When the animal was again deeply anesthetized a partial heart-block ensued, 2 to 1 in character. This was followed by a nodal rhythm previous to the recovery of the normal mechanism for the second time. Marked changes in the direction and the amplitude of the *T* wave were seen during the different degrees of anesthesia.

FIG. 7.—9.52 A.M.: A cat of 1645 gm. received intramuscularly 66 per cent of a minimum lethal cat unit dose of ouabain in oil; a small amount of ether was given to facilitate the handling of the animal; at 11 A.M. there was vomiting; at 5.32 P.M. ether was administered. 5.37 P.M.: Ekg. No. 12 (a) was taken while the cat was still slightly under the effects of ether; Leads I, II and III show nodal rhythm (no *P* wave is discernible); in Lead III there is an abrupt change in the direction of the *T* wave, and then gradually recovery to normal condition. 5.39 P.M.: Ekg. No. 12 (b) was taken as the cat was recovering from its anesthesia; this tracing demonstrates strikingly the variability in the height of *R*, *S* and *T*; nodal rhythm still persists; *T* is oppositely directed as compared with Ekg. No. 12 (a). 5.41 P.M.: Ekg. No. 12 (c) was taken while the cat was practically completely recovered from anesthesia; here *P* is distinctly returned; *T* is directed as in the first series; it will be noted that the nodal rhythm disappeared as the animal recovered from its ether anesthesia.

CHART IV.—CAT 101. ELECTROCARDIOGRAM 15 (SEE PRINTS).
DECEMBER 30, 1922.

Record No.	Time, P.M.	Electrocardiographic changes.	Anesthesia.
1-0 . .	4.00 4.15 to 4.20	<i>T</i> wave iso-electric in Leads II and III <i>R</i> wave low voltage	Anesthesia started. No anesthesia during the taking of records; eye reflexes present; moving legs; additional anesthesia was given toward end of record.
1-1, 1-2 and 1-3	4.25 to 4.32	<i>R</i> , low voltage; <i>T</i> iso-electric	Same as 1-0; the cat was deeply anesthetized and then allowed to come out.
1-4, 1-5 and 1-6	4.45 to 4.57	Low voltage more marked; slight variations in <i>P-R</i> interval	No anesthesia; no reflexes; just after Lead III cat opened eyes and moved limbs; anesthesia again given until deeply narcotized; no visible breathing during the taking of 1-6.
1-7 . .	5.03	Bradycardia; <i>P-R</i> increased to 0.2 sec.; <i>R</i> abnormal; heart-rate fell to 70; <i>P</i> not visible in Part I; <i>R</i> deflections became negative, with a large sweeping <i>T</i> —a diphasic ventricular deflection; a little later the <i>R</i> wave again became upright but no <i>P</i> oscillations were recognizable. The next strip showed entire change in mechanism; auricles were well represented, beating at the rate of 300 per minute—"auricular flutter;" the <i>R</i> was inverted during this period	Deeply under anesthesia; no breathing; tongue deeply cyanosed.
1-8 . .	5.05	A slow idioventricular rhythm with a diphasic ventricular response (negative <i>R</i> and positive <i>T</i> waves); occasional auricular wave was seen	Very little breathing; occasional gasps.
2-0 . .	5.09	Occasional <i>P</i> visible; ventricles responded as at end of 1-8	No heart sounds audible.
2-1 . .	5.11	Diphasic ventricular responses more pronounced, wider and deeper; very few auricular complexes seen	
2-2 . .	5.21	<i>R-T</i> very wide, notched and low voltage; <i>P</i> less frequent and finally it was represented as a small irregular oscillation seen at a more rapid rate and interrupted by an infrequent diphasic ventricular wave; all deflections ceased	Chest opened; occasional beat observed in the left auricular appendage.

Résumé. During the stage of what may be considered and loosely termed a "surgical anesthesia," minor changes in the electrocardiograms were noted: a slight variation in the *P-R* interval and a lowering of the voltage in the *R* wave. During deep and almost overwhelming anesthesia a heart-block developed with later a complete arrest of auricular activity and a slow idioventricular rhythm resulted. A moment after this the auricles went into a state of flutter, beating regularly at the rate of 300 per minute, the ventricles responding irregularly at about 106. This condition lasted only a short time, the auricles continued to beat slowly and infrequently, while the ventricle activity soon disappeared entirely. When all oscillations stopped in the electrocardiograms the chest was laid open and an occasional quiver was observed in the left auricular appendage.

CHART V.—CAT 146. ELECTROCARDIOGRAM 49 (SEE PRINTS).
MAY 3, 1923.

Record No.	Time, P.M.	Electrocardiographic changes.	Anesthesia.
	4.45 to 4.46	Light anesthesia begun; no records were taken.
2-0 . .	4.47	Normal; <i>T</i> upright in all three leads	Reflexes present; moving head; moaning.
	4.50	<i>R</i> wave negative in Lead I; rate, 210	Animal is allowed to come out of anesthesia completely.
3-0 and	4.51	Rate increased, otherwise no change	Eye reflexes abolished; moving head and legs near end of the experiment.
4-0 . .	4.53		As above.
5-0 . .	4.55	Rate, 105; Lead III <i>T</i> wave became iso-electric and later partly negative	Anesthesia resumed.
6-0 . .	4.58	Slightly under; eye reflexes not abolished; anesthesia increased.
	4.59	Sinus arrhythmia; <i>T</i> wave iso-electric	Anesthesia continued until deeply under.
7-0 . .	5.00	Lead II <i>T</i> wave at first deeply negative, gradually diminishing until flat, then gradually mounting upward higher and higher	
7-0 . .	5.02	<i>T</i> wave encroached upon <i>R</i> , and together they formed a curious bifid oscillation of wide nature; <i>P-R</i> interval increased gradually and a complete block followed; <i>R-T</i> combined wave became wider and the voltage lower (arborization type of deflection); no <i>P</i> wave was visible, and for a long stretch until death this slow, wide and long ventricular deflection continued	Tongue deeply cyanotic; artificial respiration at 5.01.
			Animal died.

Résumé. Under light anesthesia the only change noted was in the rate, which increased. Repeating the anesthesia and allowing the animal to recover three times, changes in the direction of the *T* wave occurred. In deep anesthesia marked abnormalities took place in the *R* and *T* deflections, producing a very striking picture. A complete heart-block soon followed and finally the auricular activity ceased altogether and the ventricles continued at a slow rate, with characteristic abnormal complexes, until the death of the animal.

Gilbert,² or other unknown factors. What we wish to stress is that in experiments with cats under ether narcosis electrocardiographic changes of varied degrees and types are easily provoked and may readily be mistaken for effect of some drug that may be under investigation.

At the outset of our work we followed the technic of anesthetizing each cat while its electrocardiogram was being taken. Very small

² Arch. Int. Med., 1921, 27, 517; Am. Jour. Physiol., 1921, 56, 475.

CHART VI.—CAT 145. ELECTROCARDIOGRAM 48 (SEE PRINTS).
MAY 3, 1923.

Record No.	Time, P.M.	Electrocardiographic changes.	Anesthesia.
1-0 and 2-0 . . .	3.50 to 3.55	Low voltage; <i>T</i> wave came off directly from limb of <i>R</i> before the base line was reached; deflections were upright in all three leads	No anesthesia.
3-0 . . .	4.01	Respiratory variations in rate; lower voltage	Ether for 1 min.; eye reflexes were present; toward end of record additional anesthesia given.
4-0 . . .	4.06	Very low voltage in all three leads; sinus arrhythmia	Anesthesia 2 min.; eye reflexes diminished; no anesthesia at end; reflexes returned.
	4.09 to 4.12	No records taken	Ether continued until deeply under.
5-0 . . .	4.12	<i>T</i> gradually increased in size and finally overshadowed by small <i>R</i> ; the heart-rate gradually slowed; <i>T</i> wave later diminished in size, reaching its previous amplitude	No additional anesthesia; no eye reflexes; Lead II strips recorded 30 sec. apart for 7 times.
	4.14	All deflections regular; later gradually a partial heart-block appeared with the falling-out of a ventricular beat from time to time; <i>T</i> wave again resumed the peculiar character as in previous record	Cat still deeply under.
	4.16	2 to 1 heart-block with <i>R</i> wave negative during the block period; finally the block became complete 6 to 1, with an abnormal high <i>R</i> and a deeply negative <i>T</i> ; ultimately no ventricular beats occurred and the auricles continued to beat slowly until death	Cat deeply under; a record was taken every 10 sec. for 5 succeeding periods.
	4.22	Cat died	

Résumé. During the light anesthesia only minor changes in the rate of the sinus stimulation were produced. This animal had an abnormal origin of the *T* wave which came directly off the stem of the *R* wave and was rather blunt. Repeating the light anesthesia caused an apparent reduction of the voltage of the *R* wave. During deep anesthesia a series of records showed: At first a remarkable increase in the height of the *T* wave which mounted gradually until it overshadowed the *R* wave. It finally reapproached its former altitude. As the animal became overwhelmingly anesthetized a partial heart-block was induced. This conduction disturbance increased gradually until it finally became complete and the ventricles took on an idioventricular rhythm, having its origin in some infra-auricular foci as shown by the marked abnormality of the deflection. Pre-agonally the ventricles ceased to beat and a slow auricular response continued until death of the animal; the respirations and heart sounds disappeared long before the electrocardiographic oscillations ceased.

TABLE II.—SIX ADDITIONAL EXPERIMENTS CORROBORATING THE EXPERIMENTS WITH ETHER AS TABULATED IN TABLE I.

Ekg. No.	Cat No.	Date, 1922.	Time of electrocardiogram.	Remarks.
1 (0-0) . . .	67	May 27	3.00 P.M.	Left ventricular preponderance; rate, 150.
2 (0-0) . . .	70	July 12	10.05 A.M.	Very low voltage in Lead I; average voltage, rate 215 in Leads II and III.
2 (0-1) . . .	70	July 12	to 10.10 A.M.	In Leads II and III rate 215; <i>T</i> much more flattened than in Ekg. 0-0 which was of good voltage; almost iso-electric.
3 (0-0) . . .	71	July 25	9.40 A.M.	All deflections upright; small voltage and regular rates; each cycle rate 215; <i>T</i> very flat.
4 (0-0) . . .	73*	Aug. 1	10.26 A.M.	In Lead I low voltage; in Leads II and III fair voltage; <i>T</i> down and <i>P-R</i> interval equals 0.08 sec.; rate, 250.
4 (0-0) . . .	73	Aug. 1	10.31 A.M.	As above.
5 (0-0) . . .	75	Aug. 8	9.50 A.M.	Low voltage in Lead I; fair voltage and <i>T</i> wave disappeared in Lead II; fair voltage and <i>T</i> inverted in Lead III; rate, 215.
6 (0-0) . . .	76	Aug. 17	10.32 A.M.	Very low voltage in Lead I; fair voltage, <i>T</i> wave flat, rate 215 to 250 in Leads II and III.
6 (0-0) . . .	76	Aug. 17	10.40 A.M.	As above; rate, 190.

* Same cat as 71.

TABLE III.—LISTING THE TYPES AND PERCENTAGES OF HEART DISTURBANCES CAUSED BY ETHER NARCOSIS.

Record No.	48	49	13	15	14	50	4	1	2	3	5	6	Total.	Per cent.
Sinus arrhythmia	⊕	⊕	2	16.8
Variations in the height of <i>R</i> and <i>S</i> waves	⊕	..	⊕	⊕	⊕	..	4	33.3
Nodal rhythm	⊕	..	⊕	⊕	3	25.0
Changes in the direction of <i>R</i>	⊕	⊕	⊕	3	25.0
Changes in the direction of <i>T</i>	⊕	⊕	⊕	⊕	⊕	⊕	⊕	7	58.3
Notching of <i>R</i> wave	⊕	1	8.3
Increase in the <i>P-R</i> interval	⊕	..	⊕	2	16.8
Partial heart-block	⊕	⊕	⊕	3	33.3
Complete heart-block	⊕	⊕	..	⊕	3	33.3
Ventricular extrasystoles	⊕	1	8.3
Auricular fibrillation	⊕	1	8.3
Auricular flutter	⊕	1	8.3
Number of disturbances	6	4	2	8	5	4	0	0	1	0	1	0	31	

TABLE IV.—ETHER ANESTHESIA.

Cat No.	Ekg. No.	Degree.	Duration.	Electrocardiographic changes.
99	13	Cat rapidly brought into deep narcosis and gradually allowed to recover to normal state	3.50 to 4.16 P.M. (26 min.)	7 electrocardiographs taken; there were no definite changes, except for slight variations in the height of R and S.
100	14 Deeply narcotized; gradually allowed to recover out of ether	4.20 P.M. (ether begun) 4.31 P.M. 4.50 P.M.	7 electrocardiographs taken; under deep anesthesia there developed a high-grade heart-block; as recovery took place a partial heart-block appeared and soon thereafter a normal rhythm interrupted by occasional extra-systoles (see prints and full protocol).
101	15	Received ether in varying concentrations; deeply narcotized Deeply anesthetized continued	Over period of 17 min. 6 min. 2 min. (longer) 8 min. (longer) 10 min. (longer) (Death of cat)	Earliest changes were low voltage in Leads I, II and III, under moderate anesthesia; bradycardia; P-R interval increased to 0.20 sec.; in Lead I P wave disappeared; R deflections were inverted, joining T wave. Auricular flutter; R wave widened and joined to T. Slow ventricular rhythm; no P wave; R and T diaphasic. Diaphasic deflections more pronounced; occasional P wave observed. R and T complex very wide and notched; occasional P wave. Finally small irregular oscillations at more rapid rate, with occasional diaphasic deflections until heart's standstill.
145	48	Light anesthesia Light anesthesia Moderate anesthesia Deep anesthesia	4.00 to 4.01 P.M. (1 min.) 4.05 to 4.07 P.M. (2 min.) 4.09 to 4.12 P.M. (3 min.) 4.14 to 4.16 P.M. (2 min.)	No abnormalities. Low voltage in Lead I. Very low voltage in all three leads; large T deflections with changes in height of T; in Lead III T and R united and assumed a diaphasic character. All deflections variable; partial heart-block (2 to 1) which soon became complete; died suddenly.
146	49	Light anesthesia Light anesthesia Light anesthesia Moderate anesthesia Deep anesthesia	2 min. 4.15 to 4.47 P.M. (2 min.) 4.50 to 4.55 P.M. (4 min.) 4.55 to 4.59 P.M. (4 min.) 5.00 to 5.02 P.M. (4 min.) (Died rather suddenly shortly after)	No effect. No effect. Leads I, II and III slow rate; T inverted in Lead III. Sinus arrhythmia. R-T assumed diaphasic character; P-R interval increased.

TABLE IV.—ETHER ANESTHESIA.—(Continued.)

Cat No.	Ekg No.	Degree.	Duration.	Electrocardiographic changes.
147	50	Very light anesthesia	3.31 to 3.33 P.M. (2 min.)	Lead I very low voltage (electrocardiograms normal without ether).
		Very light anesthesia	3.34 to 3.35 P.M. (1 min.)	Lead I low voltage.
		Slightly deeper anesthesia	4.12 P.M.	Lead I alternating ventricular extrasystoles.
		Very light anesthesia	Until 4.25 P.M. (had been given practically continuously for 50 min.)	Lead II, T diaphasic; 4.25 P.M., Lead I showed extrasystoles and low voltage (see prints); alternating extrasystoles, tachycardia; T inverted.
		Deep anesthesia	4.30 to 4.40 P.M. (2 min.)	No effect, that is, normal electrocardiograms.
		Recovered from anesthesia	4.45 P.M.	
OUABAINIZED CATS.				
67	..	Light anesthesia	3 min.	Left ventricular preponderance; rate, 150.
70	..	Light anesthesia	10 to 10.05 P.M.	Lead I very low voltage; rate, 215; Leads II and III, T wave flattened, almost iso-electric.
71	..	Light anesthesia	All deflections upright; small voltage; rate, 215; T very flat.
73	..	Light anesthesia	5 min.	Lead I low voltage; P and R increased 0.08 sec.; rate, 250.
75	..	Light anesthesia	6 min.	Lead I low voltage; Lead II, T not visible; Lead III, T inverted; rate, 215.
76	..	Light anesthesia	8 min.	Lead I low voltage; Leads II and III fair voltage; T flat; rate, 215 to 250.

NOTE.—This table is a compilation of the electrocardiographic changes encountered in the cats studied for the effects of ether upon their hearts.

amounts of ether were given by the open-cone method, with care to secure a very "light anesthesia" and to permit the cat "to come out" just as soon as the electrocardiographic records were finished. We feel, therefore, that very small amounts of ether used as an anesthetic in cats probably cause only the slight effects as described. Nevertheless, in a group of animals, one of whose series of electrocardiograms we print, it will be noted that this ouabainized animal shows nodal rhythm in its electrocardiograms while under the influence of small amounts of ether anesthetic used solely to keep the animal quiet for a very short time (Ekg. 12). The condition of nodal rhythm promptly disappeared when the ether anesthetic was removed, though ouabain was still in the animal and supposedly undestroyed. This experiment, as well as the results obtained in our study of the effects of ether alone upon the cat's heart, point to the possibility of a summated effect when ouabain

and ether are used in the same animal at the same time. This inference is not without interest in a consideration of the clinical habit of "digitalizing" patients directly before operation carried out under ether narcosis. The investigations of Lenox, Graves and Levine³ seem clear as to the effects of ether upon the human heart and our animal studies are in accord with their observations. It may not be amiss to emphasize that ether anesthesia, clinically, is administered in an inaccurate, unquantitative manner, and that as a consequence, though its effect upon the heart is striking under adequate ether inhalations, the threshold dose at which these effects appear must be uncertain and variable. The exhibition of nodal rhythm, for instance, in a cat's heart may be interpreted as a "spontaneous" normal phenomenon if it occurs in the unanesthetized animal. Despite the fact that small doses of ether seem to cause little change in the heart, disturbances so comparatively moderate as nodal rhythm and changes in the direction of the *T* wave may indicate an ether response rather than an intrinsic heart derangement, since the threshold dose for cardiac change from ether is so variable. In other words, a heart disturbance, however slight, may perhaps be caused by ether inhalation however "light" the anesthesia may seem to be. To mention but a few inconstant factors bearing upon this point, we have the amount of ether used, the degree of ether concentration, the duration of the narcosis and the general pharmacological effect of ether as distinct and a part from the direct effect of ether upon the living heart.

In six other experiments cats received ether as a brief narcotic in order to permit the taking of electrocardiographic tracings while these animals were ouabainized. Though ether effects were not studied here as a primary interest, nevertheless, our distinct impression is that here also the electrocardiographic changes from ether narcosis were similar to those detailed above. Table II indicates these results.

Conclusions. 1. Cardiac abnormalities occur promptly upon adequate changes in depth and duration of ether anesthesia.

2. These irregularities are transient and go hand-in-hand with the depth and duration of the anesthetic. Upon recovery from ether narcosis, no matter how deep, the cat's heart resumes its normal characteristics; all cardiac irregularities, striking and alarming as they may be, disappear rapidly.

3. No summated or cumulative effects are apparent.

4. Heart abnormalities appear under moderate and, nearly always, under deep ether anesthesia. As a rule, a very light anesthesia, whether brief or prolonged (forty minutes or more) causes little if any changes in the electrocardiograms. The changes appear if sufficient ether is administered, and disappear promptly

when ether inhalation is discontinued. This is so whether we start with a "light anesthesia" or a "deep anesthesia," or whether we alternate light and deep anesthesia.

5. The irregularities encountered assume many types and degrees of abnormalities. On many occasions the effects resemble, strikingly, those produced by digitalis intoxication.

THE PATHOLOGY OF FATAL MEASLES.

BY JAMES DENTON, M.D.,

BOSTON, MASS.

(From the Department of Pathology, Harvard Medical School.)

DURING the months of November and December, 1923, an epidemic of measles occurred in Panama and numerous patients were admitted to the Hospital Santo Tomas. Many of the cases were severe and 11 ended fatally. Autopsies were done in all fatal cases. In 8 of the autopsies death was due to bronchopneumonia differing in no important particular from the bronchopneumonia often observed after measles. In 3 cases death occurred so soon that bronchopneumonia of any important extent had not yet developed. From observation of the patients, from the circumstances under which they died, and from the pathological changes found, it is believed that the deaths were due to uncomplicated measles and that the lesions found are the lesions of the disease. As a fatal termination in measles during the first few hours after the appearance of the exanthem is unusual, and as the clinical symptoms point so sharply to the location of the lesions in the bronchi, brief histories of the cases are given.

Case Reports. CASE I.—A. A. (Autopsy No. 8017), a female, aged twelve years, was admitted November 24, 1923, and died the next day. Death occurred three hours after the appearance of the rash.

Clinical Résumé. The patient gave no history of previous illness or of having had the usual diseases of childhood. She was admitted on the third day of illness with these symptoms: Fever, temperature 104° F., headache, coryza, conjunctivitis, and cough. The skin was hot and dry and markedly hyperemic, the lips and finger nails cyanotic, the conjunctivæ injected, with small hemorrhages into the scleræ. The mouth and throat were red; there was no membrane on the tonsils. Koplik's spots were present. Respirations were rapid and shallow and there was a slight dry cough. Expansion was equal but somewhat restricted on both sides. The percussion

note was hyperresonant over the whole chest, there were no areas of decreased resonance, no modification of voice sounds. Inspiration was harsh and short, expiration harsh, and there were numerous musical rales over the whole chest. The heart was not enlarged, the rate was fast and slightly irregular, the pulse small. The liver and spleen were not palpable. Blood—no malaria parasites. Leukocytes 12,000. The urine showed a trace of albumin, no casts.

On the evening of admission the patient had the appearance of having severe bronchitis, except for the marked hyperemia of the skin and the cyanosis. No definite pneumonic signs were noted.

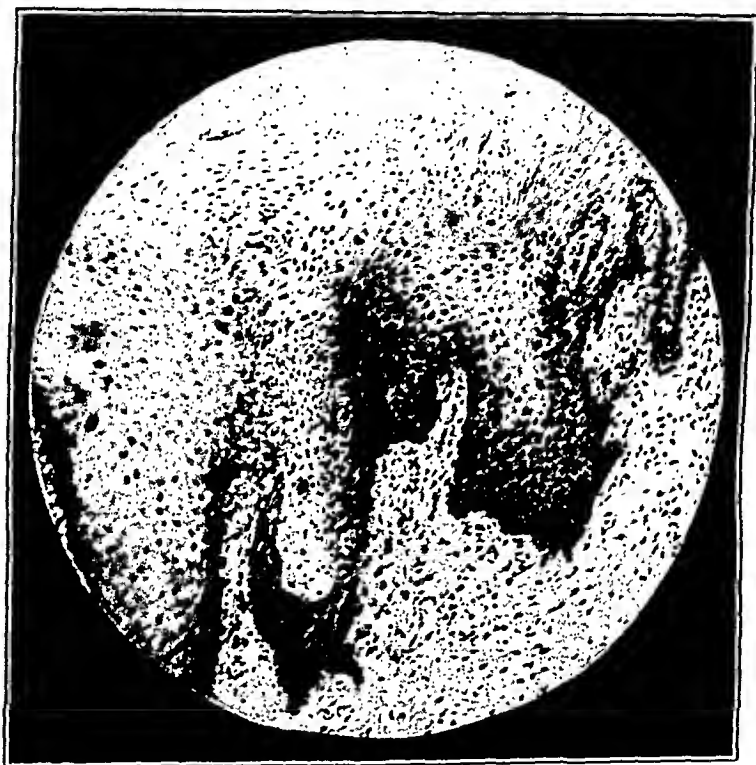


FIG. 1.—Photomicrograph of section of buccal mucous membrane, Case No. 8017, $\times 200$. Focal necroses in the epithelium with reaction in the papillary vessels.

The following morning the general cutaneous hyperemia cleared away and a bright measles rash appeared. The respiration and heart action became faster and at noon the pulse was imperceptible. Exitus 1.20 P.M.

Autopsy Protocol. Autopsy a few minutes postmortem.

Anatomical Diagnoses. Measles (exanthem); catarrhal tracheitis; capillary bronchitis; lymphadenitis (cervical and mediastinal).

The body is that of a well-developed and well-nourished girl about twelve years of age. There is a well-marked, red, macular rash on the face, neck, upper trunk and over the upper arms. The conjunctivæ are pinkish-red and a small amount of exudate is

adherent to the margins of the lids. A few small, indefinite, gray spots can be seen on the buccal mucous membrane. Ventral incision: The fat is normal in amount, the muscle is dark red. No localized areas of loss of color can be seen in the muscle and no hemorrhages into the subcutaneous tissues can be found. Both pleural cavities are free from fluid and adhesions. The thymus is normal. The right lung is increased in volume and almost fills the right pleural cavity. The consistence is slightly increased,

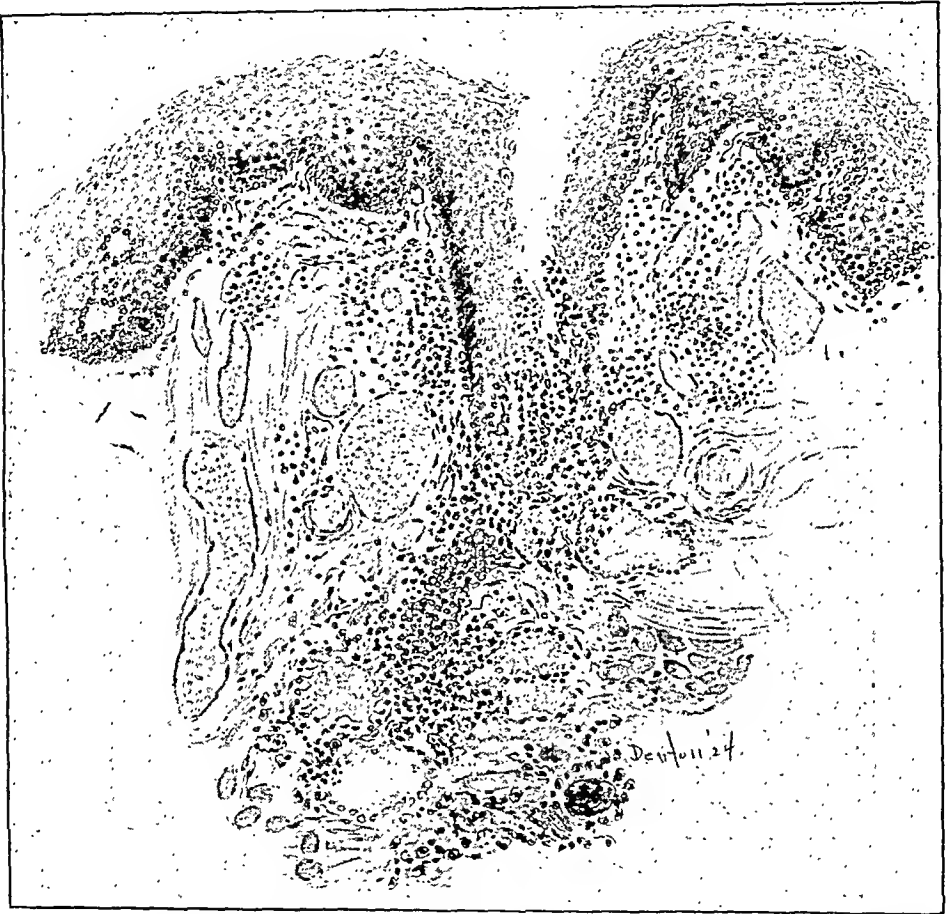


FIG. 2.—Drawing of a submucous gland from the mouth, Case No. 7976, $\times 100$. Koplik spot. Suppurative reaction in and about a gland and duct from the cheek. Note the collar-like plexus of veins about the duct. Grossly this lesion was less than 1 mm. in diameter.

the weight but little increased. The pleural surfaces are smooth and pinkish-gray except for small (pin-head sized) hemorrhages beneath the pleura. In the lower lobe there are several small, slightly depressed dark red, firm, wedge-shaped areas, none more than a centimeter in area (small atelectases). There is no fibrin on the surface. On section the cut-surface is mottled in pinkish-red and red, the mottling being due to roughly circular dark red areas about bronchial radicles of various sizes. About some of the larger

bronchi some of these have a faint gray tint. There are numerous small hemorrhages into the peripheral parenchyma. An occasional small bronchiole contains a drop of white pus. When thin slices of lung are placed in fixing fluid (Zenker's) small clusters of opaque yellow appear about bronchioles. These areas were dark red and quite translucent before fixation. The left lung is like the right. Some bronchi contain a small amount of thin white pus. The mucous membrane is pinkish-red with a few small gray flecks on the surface of some of the larger branches. The mucous membrane of the larynx is pale pink a little mucus covers the surface. Followed

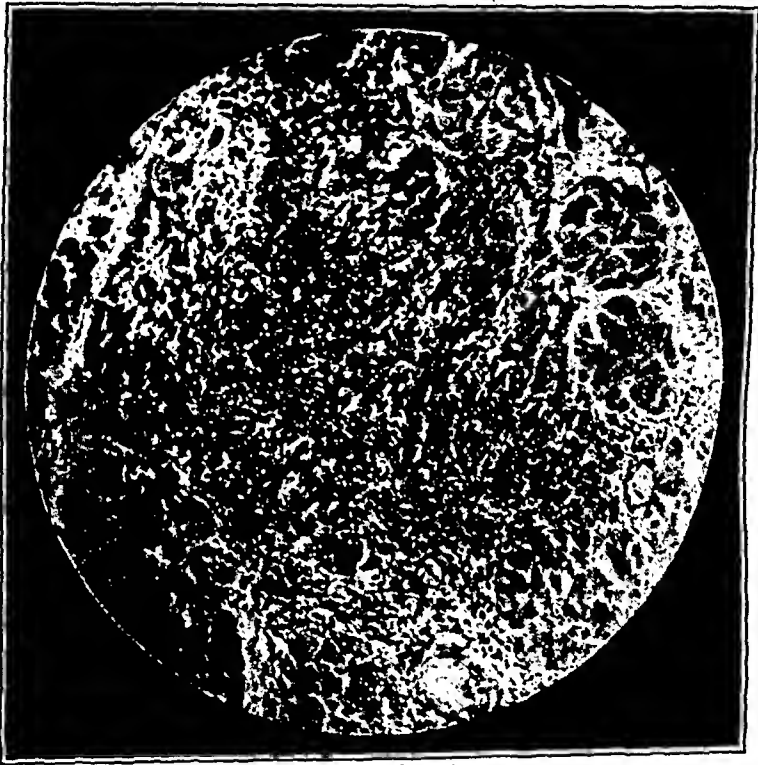


FIG. 3.—Photomicrograph of focal lesion in the muscle of the cheek, Case No. 7976, $\times 175$. Reaction in necrotic muscle at the base of a submucous gland, one acinus and a thrombosed vessel are shown.

downward the mucous membrane of the trachea becomes redder and there is more mucus on the surface. The cervical and mediastinal lymph nodes are enlarged and pinkish-gray on section. The heart is of normal size. Both auricles are slightly dilated. The valves and valve orifices appear normal. The heart muscle is dark bluish-red in color, and softer than normal. The spleen is not enlarged and is of normal consistency. On section the cut-surface is purplish-red, the follicles are small and numerous and readily visible. The liver is of normal size and brownish-red in color. Several small, light yellow ischemic areas are present

in the margins. The cut-surface is brownish-red and slightly opaque but lobular markings are visible. The kidneys are of normal size and pale red in color. On section they have normal markings. The adrenals are of normal size and normally pigmented. No hemorrhages are present in the parenchyma. The mucous membrane of the bladder is pale pink except over the trigone where it is slightly injected. No hemorrhages are present. The mucous membrane of the stomach and intestine is of normal color. No hemorrhages are present in the mucosa. The skull and scalp are normal. The bones of the cranial cavity are bluish-gray in color;

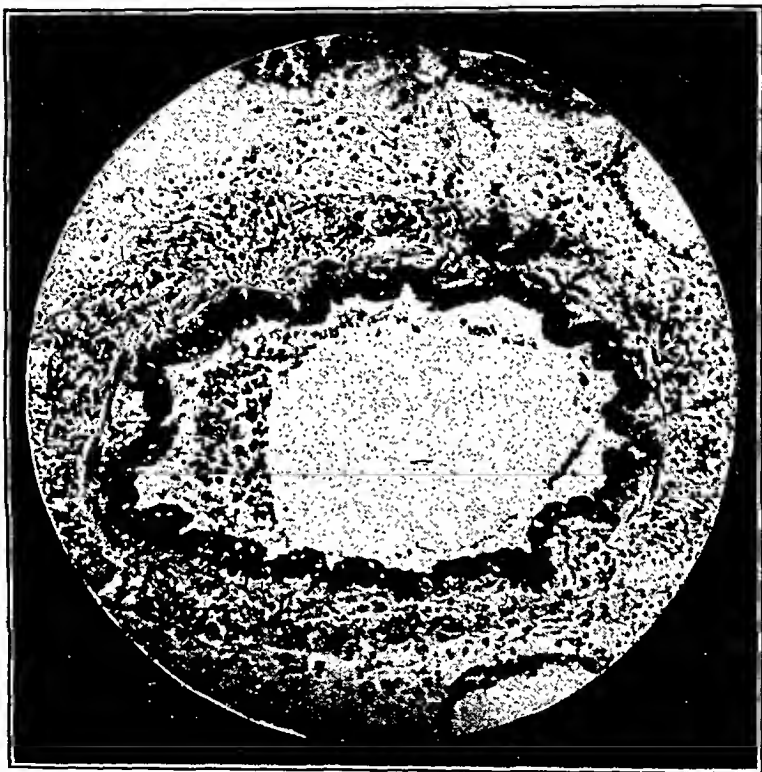


FIG. 4.—Photomicrograph of small bronchial radicle, Case No. 8017, $\times 700$. Vacuolar changes in epithelium, purulent exudate in the lumen, reaction in the wall, beginning reaction in surrounding alveoli.

the blood spaces in the cut edge of the skull cap are bluish-red. The brain is pale and everywhere the cerebral markings are very much flattened out. The pia-arachnoid contains no visible fluid, the sulci are shallow, the gyri are wide and flat. The vessels of the cortex are not prominent. The cerebral veins of the base are filled with blood.

CASE II.—I. N. (Autopsy No. 7976), a female, aged six years, was admitted November 4, 1923 and died November 8, 1923. Death occurred eighteen hours after the appearance of the rash.

Clinical Résumé. No details were available as to past history. Her symptoms on admission were: Fever, temperature 104° F., coryza, conjunctivitis and slight cough. A sister one year older was admitted the same day with similar symptoms. Examination showed a well-developed and well-nourished female child with pharynx slightly injected, conjunctivæ red. There was a thin serous discharge from the nose, and respirations were fast and noisy. There were no areas of dulness; the percussion note slightly hyper-resonant over the whole chest, with a few scattered rales. November 6: Her temperature was 104° , with slight cyanosis of lips and



FIG. 5.—Photomicrograph of bronchiole, Case No. 8017, $\times 700$. Vacuolar changes in the epithelium, endothelial and polymorphonuclear leukocytes in the epithelium and submucosa. Phagocytosis of necrotic smooth muscle in the wall.

finger-nails, but no dulness. A typical measles rash appeared on the patient's sister, admitted the same day. On November 7, a typical measles rash appeared on the patient with but little change in the physical signs. Exitus November 8, 1923.

Autopsy Protocol. Autopsy a few minutes postmortem.

Anatomical Diagnoses. Measles (exanthem); bronchopneumonia (early); catarrhal tracheitis; capillary bronchitis; lymphadenitis (cervical and mediastinal).

The body is that of a well-developed and well-nourished female child about six years of age. There is an extensive papular rash

over the face, chest and upper arms. On the face the papules are very readily palpable. In the ventral incision, the fat and muscle are normal in amount and color. No hemorrhages are visible in the soft tissues. Both pleural cavities are free from fluid and adhesions. The whole left lung is increased in volume. The pleural surfaces are smooth and mottled in red and faint gray. The lymphatics beneath the pleura are prominent as gray lines. The cut-surface is mottled in red and faint gray; the gray areas are in the form of indistinct rings and clusters about small bronchial radicles. Very little exudate comes off the cut-surface, a few small

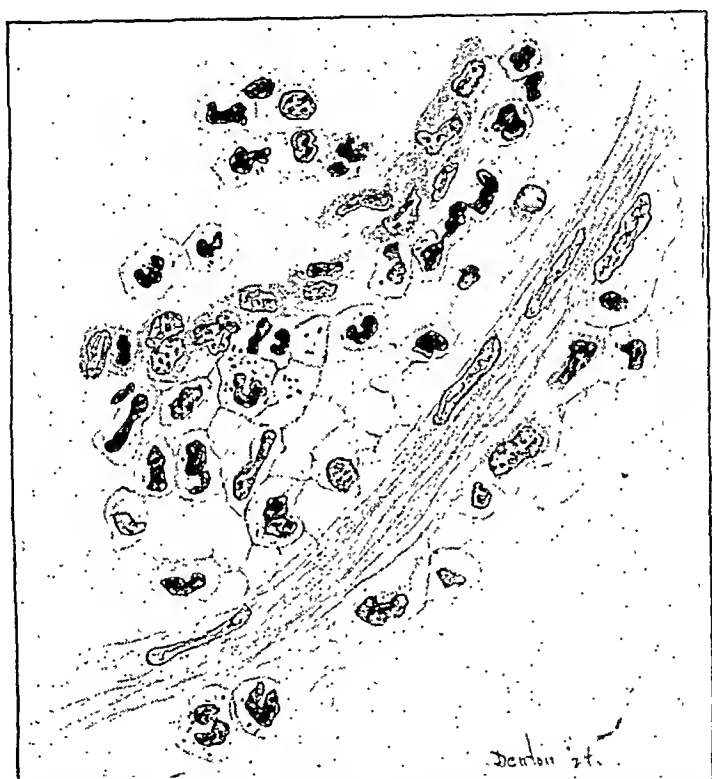


FIG. 6.—Camera lucida drawing of a section of a small bronchial radicle, Case No. 8017, $\times 900$. Small single and paired bacilli within leukocytes in the lumen and in the submucosa.

beads of pus appear on slight pressure. The lower lobe is somewhat firmer than the rest of the lung and the gray areas about some of the bronchi are more distinct. The right lung is like the left. The bronchial mucous membrane is covered with mucopurulent material and on removing this the mucous membrane is rose-red in color. The larynx and trachea contain mucopurulent exudate, the mucous membrane is injected throughout. The lymph nodes of the neck and mediastinum are enlarged, pinkish-gray and rather soft in consistence. No changes are visible in the remaining organs.

CASE III.—G. L., (Autopsy No. 7997). A female, aged one month and twenty days, was admitted November 22, 1923, and died the next day, twenty-four hours after the appearance of the rash.

Clinical Résumé. The child was brought to the hospital suffering with rapid breathing, coryza, conjunctivitis and a recent, typical measles rash. Two other children from the same family and living in the same rooms were admitted a few days previously with measles. No definite physical signs were noted in the child's chest on admission. During the night the respirations became more rapid; exitus occurred eight hours after admission.

Autopsy Protocol. Autopsy one hour postmortem.

Anatomical Diagnoses. Catarrhal tracheitis; bronchopneumonia (early); capillary bronchitis; lymphadenitis (cervical and mediastinal).

The body is that of a well-developed and well-nourished female child about two months old. The skin of the face, chest, shoulders and upper arms contains numerous small, red macules and indistinct papules which in places are confluent. No gross lesions in the buccal mucous membrane are seen. In the ventral incision the fat and muscle appear normal. There are no hemorrhages in the subcutaneous tissues. No fluid is present in the pleural cavities. Both lungs have the same appearance; their volume is slightly increased. There is no fibrin on the pleural surfaces. Underneath the pleuræ there are numerous, small, red points of hemorrhage. The consistence is slightly firmer than normal. On section the cut-surfaces are mottled in red and pinkish-red. Very indistinct gray areas are visible about some of the larger bronchi. An occasional bronchiole contains a small drop of pus. A section down through the trachea and bronchi shows a uniformly red mucous membrane covered in places with scanty, mucopurulent exudate. The lymph nodes in the neck and at the bifurcation of the trachea are enlarged and pinkish-gray on section. The other organs show no significant changes.

From a clinical point of view these cases are very similar to other cases observed during the epidemic. The symptoms and physical signs observed in these cases were also noted in cases which terminated in recovery. They indicate primarily interference with respiration and accumulation of carbon dioxide in the blood.

Histological Examination of Tissues. No changes referable to measles have been found in any organs except the skin, mouth, pharynx, trachea, bronchi and lungs. The changes in the respiratory tract are very similar in the three cases, the variations being very slight and simply a matter of degree. A careful search has been made in sections of numerous simple tissues for disseminated vascular lesions such as one would suspect if the virus of the disease circulates in the blood. No lesions of this type have been found.

The Skin. The changes in the skin agree with the accounts

of the skin lesions given by Ewing¹ and later by Mallory;² the lesions consist in moderate hyperemia and edema of the corium with degenerative changes in the epidermal cells. The endothelium of the capillary and precapillary vessels of the corium show rather marked swelling and proliferative reaction. Mitoses in capillary endothelium and in that lining small veins are fairly numerous in the early hours of the rash. Accumulation and proliferation of endothelial leukocytes about the vessels are more prominent in the second and third days of the rash. From study of the skin obtained at autopsy and excised during life in numerous cases it seems very clear that the changes in the epidermis are secondary to those in the capillary and vascular endothelium. The skin lesions do not show any evidence of being infectious in nature, beyond the proliferative activity on the part of the endothelium. Thrombi have never been found in the specimens examined. Very similar changes have been observed in toxic rashes which obviously had no relation to measles. Various, small, globoid and rod-like bodies have been seen within the endothelial cells and about the bases of cells of the basal layer, but none of them have had sufficiently definite morphological characters to warrant regarding them as microorganisms. Bodies of the type described by Mallory² have been observed, but is impossible to add more than conjecture as to their nature. All these things seen in the skin have been more numerous in the second and third days of the rash.

Mouth and Pharynx. There are three types of lesions in the mouth and pharynx. (1) Small collections of endothelial and polymorphonuclear leucocytes in small necroses of the epithelium. Beneath these necroses there is reaction in the endothelium of the papillary vessels. They appear to start in the epithelium and later, sloughing causes the formation of a small ulcer. (2) Suppurative lesions of small submucous glands and their ducts. (3) Inflammatory lesions of small submucous lymph follicles. The second lesion is of interest for two reasons. The typical Koplik spot is surrounded by bluish and red zones. From the comparative constancy in location of the Koplik spot it seems clear that it must originate in a rather constant anatomical structure. For this reason and on account of its size there is little question that it originates in a submucous gland. The ducts of each one of these glands is surrounded by a collar of dilated veins and these offer ready explanation of the bluish halo about the spot. Most of the focal lesions found in the buccal mucous membrane are so small that they would hardly be grossly visible at the time of or before the appearance of the exanthem. Some lesions found several days after the appearance of the rash are large enough to be seen with the unaided eye. The suppurative reaction in the glands frequently extends beyond the limits of the glands and leukocytes accumulate about the margins. In Case II there is reaction in necrotic muscle of the cheek with

thrombosis of small vessels, which is interesting on account of its obvious relation to noma. Noma, by the way did as a matter of fact, cause the death of two children in the epidemic from which this material was gathered. Lesions have not been found in the buccal mucous membrane which give any evidence of being due to a blood-borne virus. All those found appear to be due to extension from the mucous surface. No sections have been made from the lips and gums and it is therefore impossible to express an opinion as to the presence of herpetic lesions there.

Larynx and Trachea. Throughout the larynx and trachea the mucous membrane is edematous and groups of superficial cells and solitary deeper cells are undergoing degenerative and vacuolar changes. The vessels of the stroma and submucous tissue are dilated, the endothelial cells are large and many are undergoing cell division. About the vessels and in the stroma are large numbers of endothelial leukocytes, plasma cells, lymphocytes and small numbers of polymorphonuclear leukocytes. This increase in cell elements is partly due to inflammatory reaction and partly to increase in size and number of cells of the lymphoid stroma of the upper respiratory tract. The ducts of submucous glands are filled with desquamated epithelium and leukocytes. The acini of many glands contain leukocytes and countless numbers of a small, Gram-negative bacillus. These organisms are also present in numbers in the perinuclear vacuoles of epithelial cells. Other bacteria are very few in number. In the stroma about many of the submucous glands are areas of reaction with endothelial and polymorphonuclear leukocytes. The lymph nodes at the lower end of the trachea show marked inflammatory changes. The sinuses contain large numbers of plasma cells, large phagocytic cells and small numbers of polymorphonuclear leukocytes. The endothelial cells lining the sinuses are large and often contain mitotic figures.

The epithelium of the trachea is everywhere intact, degeneration of epithelial cells being limited to solitary cells and small groups of superficial cells. Active regeneration of epithelial cells is evident by the numbers of mitotic figures in dividing cells. The changes in the stroma are more marked than those in the epithelium as the reaction must necessarily take place from back of the epithelium. In general the inflammatory reaction is much more mild than in the cases described by Ewing.¹

Bronchi. The changes in the bronchi are much like those in the trachea but complicated, in places, by rather extensive destruction of epithelium. Here again the lesions are primarily in the epithelium, but reaction can only take place from the back. In the larger bronchi the epithelium is thicker than normal and there are more layers of cells than normal. The epithelium is generally intact, only individual cells undergoing vacuolar degeneration with the formation of small, clear spaces in the epithelium. Neighboring cells may be

well preserved, oversized or dark-staining with mitotic figures and atypically arranged chromatin. In the small cavities left by degenerating epithelial cells are small groups of two or more leukocytes and straggling ones between the epithelial cells. On the surface there is in places a small amount of purulent exudate and small masses of mucus, but no fibrin. Both the leukocytes and mucus contain numbers of this same small bacillus. Practically no other organisms are present. The walls of bronchi are considerably thickened by dilated vessels lined with large endothelial cells and by numbers of endothelial leukocytes, plasma cells, lymphocytes and small numbers of polymorphnuclear leukocytes. Small veins and lymphatics often contain numbers of large mononuclear cells and fibrin, but no thrombi.

In the smaller bronchial radicles the epithelium is not generally necrotic but in places is raised off the connective tissue backing with endothelial leukocytes and pus cells beneath it. Long tags of well-preserved epithelium, detached from bronchial walls lie in open spaces surrounded by leukocytes.

In many bronchioles the wall cannot be made out, for it often shades off into swollen, contiguous alveolar walls. In places, alveoli close to bronchial radicles contain large mononuclear cells from the respiratory epithelium and fused sheets of atypical respiratory epithelium. Numerous giant cells with five to twenty nuclei and well preserved or degenerating cell bodies are present. A group of alveoli close by may contain pus cells and erythrocytes with but little or no fibrin. Dark-staining compact masses of polylobate nuclei, between which no cell boundaries can be seen lie in some alveolar spaces. In numerous alveoli and infundibula the exudate has the appearance of having been aspirated. Purulent exudate and short cylinders of infundibular epithelium lie in spaces where the respiratory epithelium and bronchiole show no reaction.

It was anticipated that some of the dark-red areas seen grossly would have some relation to small arteries of the lung and that changes in the precapillary vessels more or less analogous to the changes in the cutaneous vessels would be found but this relationship has not been established. The areas of reaction in the lung are purely peribronchial in distribution and the only vascular lesions found have been in the small vessels beneath the epithelium in the bronchi and in small veins in the septa draining penumonic areas.

The actual extent of the bronchopneumonia is limited and the primary injury to the lung is apparently not very severe. The reaction, except in areas where the exudate has pretty definitely been aspirated, is mononuclear in type and made up of endothelial leukocytes, lymphocytes and large phagocytic cells from the respiratory epithelium. The sheets of fused epithelial cells and the formation of large giant cells represent a process of some days' duration and imply a rather weak injurious agent.

There seems to be no question that the organism found in this material is responsible for the lesions present a few hours after the appearance of the exanthem. This influenza-like organism is readily distinguished from Gram-positive organisms, such as pneumococci and streptococci, by the use of Goodpasture's stain as modified by MacCallum. The staining reaction of the organism is somewhat different from Gram-positive organisms in Giemsa preparations. The absence of other organisms in the lesions is additional good evidence of the importance of this organism in the lesions.

The eight cases in which death resulted from pneumonia later (six to twenty days after the rash) are entirely comparable to the cases described by MacCallum.³ In these cases Gram-positive organisms are demonstrable in the tissues and the Gram-negative bacilli are still present in some of them. The term interstitial bronchopneumonia very aptly describes the pneumonia in the later cases and it is a very logical result of the lesions found in the earlier cases. Post-measles pneumonia cannot be regarded as an accidental complication of measles but, the extension of a process well started when the exanthem appears. Reaction in the bronchial walls, which in many situations implies also reaction in the framework of the lung, is the only way in which reaction can take place in inflammation of the bronchial mucosa. The transportation of the organism found in these cases from the mucous membrane along septal veins and lymphatics readily explains the interstitial location of some of the lesions found in later cases as Gram-positive organisms would be transported along the same paths.

The lesions in the trachea and bronchi are very similar to but less intense than those described by Ewing and it would be difficult from a study of the cases to come to any other conclusion than that arrived at by him, namely, that there exists in measles, "infection by a rapidly multiplying microorganism of the class of bacteria." Clinically the changes in the respiratory tract give good evidence of their existence four or five days before the exanthem. The pathological changes are confined to the respiratory tract and largely to the epithelium and they indicate that the morbid process is located there.

Summary and Conclusions. (1) In these 11 postmortems on subjects dead of measles, death was due in all probability, in 3 cases to the virus of measles.

2. The primary lesions of measles are located in the lower trachea, bronchi and contiguous lung.

3. There are three types of lesions in the buccal mucous membrane: (a) Reaction in focal necroses in buccal epithelium; (b) suppurative lesions in and about submucous glands and their ducts; (c) inflammatory lesions of submucous lymph follicles.

4. The Koplik's spot is an inflammatory lesion of a submucous

gland and the bluish halo about it is due to the collar-like plexus of venules about the duct.

5. The Gram-negative bacillus found in the lesions in these three cases has every appearance of having etiological relationship to measles and deserves further investigation.

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RETROPHARYNGEAL LYMPHADENITIS IN INFANCY AND EARLY CHILDHOOD.

BY STAFFORD MCLEAN, M.D.,

NEW YORK CITY,

AND

FREDERICK H. VON HOFÉ, M.D.,

SOUTH ORANGE, N. J.

(From the Babies' Hospital, New York.)

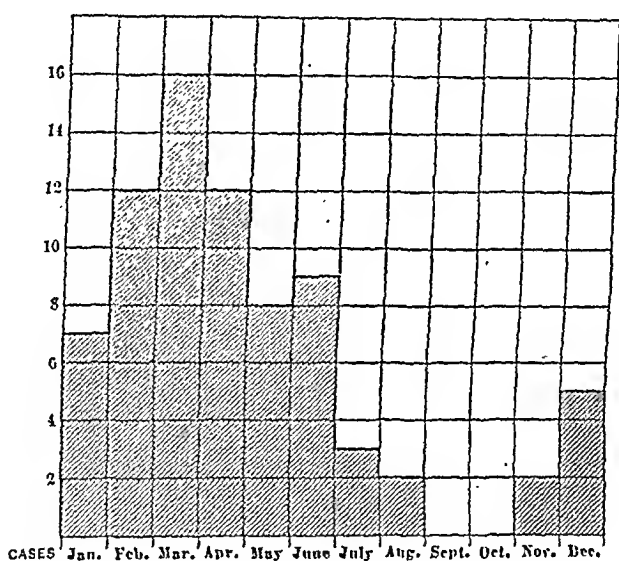
RETROPHARYNGEAL lymphadenitis is one of the frequent causes of the hospitalization of infants during the winter months. It is a condition which may be readily recognized in most instances, but in our experience the diagnosis is often delayed even until the onset of alarming symptoms. Although the term retropharyngeal swelling unfortunately seems to convey the loosely applied meaning of abscess, it is reasonable to suppose that the retropharyngeal lymph glands may become infected and enlarge as frequently as the glands of the cervical chain, suppurating in only a small percentage of cases, as do the cervical glands. Judging by the mild symptoms in some cases of retropharyngeal lymphadenitis seen by us, it may be inferred that the condition occurs with greater frequency than is believed.

For a complete study of the etiology, anatomy and pathology of the condition, with a survey of the literature, the reader is referred to an excellent article by Frank.¹ A study of the following 77 records of infants and young children with retropharyngeal swelling admitted to the wards and out-patient service of the Babies' Hospital during the past ten years seems to yield data of sufficient interest to merit publication.

The youngest case occurred in an infant, aged two months, and the oldest in a child aged four years. Twenty-three of the cases were in infants not over six months of age, and 19 between the

ages of six and nine months. Fifty-five cases, or 71 per cent, were not over twelve months of age, which corresponds with the age incidence given by both Bokai² and Holt and Howland.³ That even very young infants do not escape the disease is proved by its occurrence in 4 cases not over four months of age.

As noted in the accompanying chart the prevalence of retropharyngeal lymphadenitis follows closely the curve of the respiratory infections, being highest in the late winter and spring with an abrupt decline at the approach of summer. Season, however, does not entirely exclude the possibility of the disease, as shown by the appearance of several cases in June and a few in July and August. (See Chart.)



Seasonal incidence of retropharyngeal lymphadenitis.

Although the average child admitted to the wards of the Babies' Hospital is undernourished and underdeveloped, and generally has a history of difficult digestion, poor hygiene and neglect, the cases of retropharyngeal lymphadenitis seemed to be exceptions to this general classification, as will be noted in the following: Among 58 cases, in which there were careful notes by the examining physician regarding the nutrition of the child at the time of admission, 48, or 83 per cent, were described as well nourished, and the balance showed varying degrees of malnutrition. It seems fair to assume that a rhinopharyngitis must have preceded the involvement of the lymph nodes in the majority of cases, yet the inference may be drawn that it is not usually of great severity, as in only 9 of the patients admitted had this been sufficiently marked to impress the family with its importance as a possible etiological factor. The presumption is that retropharyngeal lymphadenitis may occur with equal frequency as a complication of a mild or a severe upper respi-

ratory infection. The symptoms which impressed the parents of 40 of the patients as being sufficiently grave to warrant hospital relief, were some deviation from normal respiration. In most of this group it was described as "difficult breathing," in a few as "noisy breathing," in one "harsh breathing" and one parent stated that the child had become "short-winded." Of the 77 cases, in only 4 was the sole complaint "difficulty in swallowing," while 2 of the 40 cases previously mentioned had difficult deglutition in addition to respiratory difficulty. Frank makes the observation, which has also been noted by others, that when the swelling is high in the pharyngeal wall there is no interference with respiration, but difficulty with deglutition is usually noted. If the swelling is low in the throat the respiratory difficulty becomes prominent. He quotes Symington, who observed that, though the neck as a whole is relatively longer in children than in adults, the larynx in infancy is fully one vertebra higher in position.

In 25 of the patients swelling of the neck had been noted by the parents as a precursor of difficult deglutition or embarrassment of respiration, or had appeared coincidently, or was the only symptom observed. The appearance of swelling of the neck, due to cervical adenitis, in 1 of every 3 patients draws attention to the importance of carefully excluding an associated retropharyngeal lymphadenitis in every child with cervical lymphadenitis. On admission to the hospital, 56, or 73 per cent, of the cases had cervical lymphadenitis. In 27 of these the swelling was bilateral, and in several it was very extensive. As a commentary on the chances of liquefaction of the glands, and this would seem to hold good for either cervical or retropharyngeal glands, in only 4 of the group of 56 with cervical adenitis did demonstrable liquefaction of the cervical glands occur. In other words, the chances of glands in that region suppurating after infection is apparently only 7 per cent.

It would seem when with upper respiratory infections one gland becomes infected, there is apt to be a reaction of the neighboring lymph glands.

As further evidence of this, the figures for involvement of the tonsils may have a bearing. Among 45 cases in which a careful examination of the tonsils was made at the time of admission, 35, or 77 per cent, were enlarged. Of the remaining 10 cases, 4 had had tonsillectomies, 2 were described as congested and the balance were normal. There was no variation between the frequency of involvement of the right and left side of the retropharynx. In 1 case the swelling involved both sides of the pharynx, probably as a result of infection of several retropharyngeal glands. In 3 cases the swelling seemed to be directly in the midline.

The extent of the temperature reaction is apparently not a guide to the severity of the symptoms, as only 27 of the cases had a temperature above 100° F., and of these but 14 were 103° F. or above.

The blood picture showed a reaction out of all proportion to the rhinopharyngitis, which usually precedes and accompanies the disease. The leukocyte reaction, however, could not be used as an aid in differentiating the stages of infective lymphadenitis, that is, before or after suppuration, as the total counts in some of the former were as high as in the latter. In 35 cases of retropharyngeal lymphadenitis, in which leukocyte and differential counts were made, the average was 20,700 per c.mm., with a polymorphonuclear neutrophilic average of 68 per cent, as contrasted with 18 unselected cases of simple uncomplicated rhinopharyngitis or rhinitis, in which the average leukocyte count was 12,900 and the average of polymorphonuclears was 50 per cent.

As mentioned previously, the number of lymphadenitis cases in our collection which proceeded to suppuration can hardly represent or be taken as an index of the frequency of suppuration in infective retropharyngeal lymphadenitis, since it is our belief that many cases of simple lymphadenitis retrogress spontaneously, unrecognized as such. The recorded cases with severe symptoms, most of which suppurated and were hospitalized for that reason, therefore give us no data as to the frequency of suppuration. However, of 74 cases on which records are available, in 7 or 9.5 per cent the retropharyngeal lymphadenitis subsided spontaneously without treatment, and these 7 patients were discharged either improved or cured of the condition for which they were admitted. The infants of this group were from two to twelve months of age. This is of special interest, as it demonstrates that the aforementioned glands may resolve at any age of infancy. It also suggests the advisability of delaying surgical interference in all cases until there is a certainty of suppuration and ample opportunity is allowed for the glands to resolve. The following history illustrates this type of case.

Case Reports. M. M., a nursing infant, aged five months, was admitted to the Babies' Hospital, March 25, 1918. The chief complaint was "inability to swallow." One week prior to admission it was noted that the infant had "difficulty in nursing." "Whenever she attempts to nurse she strangles, and is unable to swallow the milk." She was very hungry during the entire week, there was no vomiting, starvation stools were observed, scanty urine and a weight loss of 2 pounds. Fever had not been noted. The physical examination showed a moderately well-nourished infant, who appeared acutely ill. Retraction of the neck, and a hoarse cry was noted. A mucopurulent discharge from both nostrils was present; the tonsils were congested and slightly enlarged. The pharyngeal wall on the right side was thickened and indurated with moderate bulging into the pharynx. A large amount of adenoid tissue was present. In attempting gastric gavage by the nasal route it was found impossible to pass the stomach tube

through the right nostril, and with difficulty it was passed through the left. To combat the dehydration frequent hypodermoclyses were given, and gastric gavage was continued for several days. The stools shortly became fecal in character, the hoarseness disappeared, the swelling in the right pharyngeal wall gradually subsided, but could still be felt seven days after admission. The temperature at the time of admission was 102.5° F.; it rapidly subsided however, and five days later the patient became afebrile. The leukocytes were 14,200, with 60 per cent polymorphonuclears. The patient was discharged without operation, cured of the condition for which she had been admitted.

In 67 of the cases the retropharyngeal lymphadenitis advanced to the stage of suppuration. Of the 67 cases which suppurred, 4 ruptured spontaneously and a fifth was accidentally ruptured during a digital examination. In 1 of the 4 which ruptured spontaneously the opening was subsequently enlarged to favor drainage. Although spontaneous evacuation is properly considered a dangerous accident because of the possibility of aspiration of pus into the air passages, we have never observed any bad results following spontaneous rupture. Of this subgroup of 5 cases, 4 were discharged cured and the fifth improved of the condition for which they were admitted to the hospital.

One of us recently had under our care a well-nourished girl, aged three years, with a large left-sided, rather low retropharyngeal abscess occurring as a complication of scarlet fever. As this occasioned no symptoms except difficulty in swallowing it was thought advisable to delay interference until there was more complete liquefaction. On examination late one evening it seemed to have reached the stage of maximum softening; the following morning it had completely subsided with entire relief of symptoms. The inference is that it ruptured spontaneously and the pus was swallowed.

Fifty-five of these 67 cases with suppuration were incised internally and 3 externally. Only once was it necessary to reincise because of inadequate drainage. Of these, 43 were discharged as cured and 14 improved; of the balance the data was incomplete, that is, 57 were relieved of the symptoms for which hospital admission was sought, 1 was removed against advice and 7 died. Of the cases which terminated fatally, 1 was cured of the retropharyngeal abscess but subsequently died of laryngeal diphtheria; another died of a complicating bronchopneumonia.

The following case is rather typical both in history and course of the average suppurative type which terminates favorably. This case, however, was not recognized by an experienced observer in the out-patient department, who attributed the respiratory difficulty to a pulmonary infection. Al. Pet., aged twenty-two months, showed a moderate degree of malnutrition, considerable inspiratory stridor with retraction of the episternal notch, pallor,

sweating and guttural voice. The right cervical lymph glands were swollen; the tonsils were red and swollen and were pushed well forward. A retropharyngeal swelling the size of a walnut was observed at about the level of the tonsils on the right side. This was incised, and a large amount of pus obtained. A few hours following the operation the child was observed to have great difficulty in breathing. A direct smear from the abscess showed streptococci. The symptoms above mentioned rapidly subsided, and the child was discharged four days later cured of the condition for which he was admitted.

The following case illustrates the type most likely to escape recognition. Doubtless many such cases go on to recovery with incorrect diagnoses.

A. P., aged fourteen months, a well-developed and well-nourished infant, was brought to the out-patient department because of the swelling of the cervical region and slight fever. The swelling began on the left side and slowly subsided; subsequently the right side became involved, as noted on admission.

Slight interference with respiration was observed on admission; the tonsils were swollen, red and cryptic, and a small rather hard mass could be felt in the posterior pharyngeal wall. The retropharyngeal lymphadenitis gradually became more marked, and four days after admission it reached its maximum size. It then gradually subsided without interference, and twelve days after admission the child was discharged cured of his retropharyngeal lymphadenitis, but the left cervical lymph nodes were still slightly enlarged on discharge. Although no liquefaction was demonstrated, the blood examination showed 21,000 leukocytes with 81 per cent polymorphonuclears.

One infant died in the out-patient department directly following incision of the abscess, which was preceded by a digital examination of the pharynx by several of the staff. A child died in the hospital during a similar digital examination the day following incision of the abscess. It was reported to one of us that a child died recently in a Canadian hospital directly after repeated digital examinations.

Another case in our group was resuscitated with great difficulty following the same cause. The fatal results in the three cases enumerated, and the alarming symptoms in the fourth following so closely upon excessive digital examination, seem to decidedly emphasize its dangers.

Digital examination is necessary in some cases to determine whether lymphadenitis is present, and in others to determine whether fluctuation is present. Such examination should be conducted with the utmost speed and the minimum trauma. In many cases the swelling can be seen with the aid of a good light if the tongue is firmly depressed with a metal tongue depressor. From its size and appearance it can often be determined whether it has

suppurated. Digital examination is in our opinion contraindicated if the desired information can be obtained without it.

Whether the deaths in the cases under the above-mentioned circumstances were due to cardiac failure or cerebral congestion with hemorrhage or to other causes has not been determined by us. The death in one of the cases may probably be explained by the following: L. M., aged twenty-three months, was admitted to the Babies' Hospital, February 29, 1920. The chief complaint was "difficulty in breathing, increasing each day for ten days, and child had a cold two weeks ago." This was followed by a swelling of the right side of the neck; later marked respiratory difficulty was observed. The physical examination showed a well-nourished, well-developed boy, with considerable difficulty in breathing, inspiratory in type. A small swelling could be felt on the right side of the pharynx, behind the tonsils. The evening of the day of admission respiratory difficulty became more marked. At 11 P.M. the mass was opened with a hemostat, and about 1 dram of pus evacuated. Only slight relief was obtained. The following morning a mouth gag was introduced and the pharynx was examined with the finger. During the examination respiration ceased and efforts at resuscitation failed. Status lymphaticus was disclosed at autopsy. The findings were hyperplasia of spleen, lymph nodes, solitary follicles and Peyer's patches of the intestines.

As evidence that retropharyngeal lympharyngeal lymphadenitis, whether suppurative or non-suppurative, can but rarely be tuberculous except when it is secondary to tuberculous caries of the vertebræ, the following figures relating to the Pirquet test are presented: In 38 cases in which a Pirquet test was done, only 5 showed a positive reaction. This gives a rate of 13 per cent, which is less than the general average of the sick children admitted to the hospital, which in a recent analysis of 3742 cases showed 15.3 per cent to be positive.⁴ Some significance may be attached to the possibility of a tuberculous gland infection in an infant, aged eleven months, who showed an extremely well-marked Pirquet reaction. This child had pertussis two months prior to admission to the hospital. Although he was discharged cured of the retropharyngeal abscess, the history and Pirquet reaction was suggestive especially when it is recalled that occasionally the pharyngeal tonsil is tuberculous.⁵

It is difficult to obtain proper cultures in a struggling infant after it has been subjected to an operation without an anesthetic. In 21 cases, however, satisfactory cultures were made at the time the abscess was incised. In 15 streptococci were demonstrated, either alone or associated with other organisms—usually staphylococci, evidently a contamination from the mouth. In 5 of the 15 cases a non-hemolysing form of streptococcus was obtained in pure culture and in 3 the *Streptococcus hemolyticus*. All of these 8

cases recovered. In 3 cases staphylococci were the only organisms which grew. In 1 case there was a triple infection of staphylococci, pneumococci and influenza bacilli; in 2 others the pneumococcus and staphylococcus were combined.

At the Babies' Hospital retropharyngeal abscesses are opened internally by passing the instrument into the mouth directly back to the posterior pharyngeal wall unless the abscess burrows laterally, and fluctuation is present externally. One case in the above group which was incised internally had in addition an external incision over the fluctuating area. Three others had only an external incision. Two of these cases were discharged cured and the others improved. The usual procedure is to insert a moderately pointed artery clamp into the abscess and withdraw it with the blades open. The finger is used as a guide to locate fluctuation, and to direct the artery clamp to the softest point. The mouth is held open with a tongue depressor in infants, and with a mouth gag in older children.

Summary. In a group of 72 cases of retropharyngeal lymphadenitis in infants and young children on which the end-results are known, including those which subsided spontaneously, those which broke down and ruptured spontaneously, and those which were incised, the mortality was 9.7 per cent. If the 7 non-suppurating cases are excluded the mortality rate was 10.7 per cent, which approximates the mortality rates reported by others.

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STUDIES IN GASTRIC ANALYSIS (DOUBLE SIMULTANEOUS FRACTIONAL ANALYSIS).

BY RICHARD T. ELLISON, M.D.,

ASSISTANT, STOMACH CLINIC, JEFFERSON HOSPITAL; ASSISTANT PHYSICIAN, PRESBYTERIAN HOSPITAL, PHILADELPHIA.

(From the Stomach Clinic, Jefferson Hospital, Philadelphia.)

It seems almost presumptuous to attempt to add anything to the already large literature on the use of the fractional method of gastric analysis. However, the appearance in that literature during the past few years of papers by Gorham,¹ Wheelon,² Kopeloff,³ White⁴ and Friedenwald *et al.*,⁵ criticising the method through a

misconception of its fundamental assumptions and the physiological facts underlying these seemed to warrant the following contribution.

To review briefly these papers: Gorham says "The quantitative determination of the variation of gastric acidity during the different phases of digestion by the so-called 'fractional method of gastric analysis' is presumably based on the assumption that the gastric chyme after a test-meal is a homogeneous mixture and that a small portion, aspirated at fifteen-minute intervals, represents the acid concentration of the gastric contents as a whole at that period of digestion." He then showed by rapidly extracting 10-cc amounts forty-five minutes after a test-meal that there was marked variation in the acid values of the different samples, and concludes that "The true fractional analysis necessitates the giving of successive test-meals and extracting them at different periods."

Wheelon also states that fractional gastric analysis is based on the assumption that the gastric contents is a homogeneous mixture. He then proves that this is not so by a study of the acidity of samples obtained by the method of rapid divided extractions at one hour. He concludes that "A correct analysis of gastric activity can only be made when it is known (1) from what portion of the stomach the tube is delivering, (2) whether or not duodenal regurgitation is occurring, (3) the degree of motility of the stomach, (4) the secretory power of the stomach, (5) the effects of withdrawal on the motility and secretory function."

Kopeloff has done the most interesting work. He first studied the acidity of samples obtained by the method of rapid divided extractions, and found that there was considerable variation even in normal individuals. He states "The fraction obtained at any one moment cannot, therefore, be accepted as representative of the total gastric contents, for it is entirely dependent on the position of the tip of the tube in the stomach at the moment of withdrawal. Obviously, this position is necessarily a constantly changing one, due: (1) To the change of size and position of the stomach while emptying itself through the pylorus and by aspiration; (2) the shortening and lengthening of the stomach from gastric contraction; (3) the peristaltic waves that tend to carry the tube toward the pylorus." He then introduced three tubes into the same subject—one to a distance of 50 cm., one to a distance of 45 cm. and the other to 40 cm. Extractions were made simultaneously from each tube and fractional curves plotted. This was done on 3 patients. In discussing the results he says: "The fraction taken from the tube inserted to 40 cm. is almost invariably lower in total and free acidity than the fractions taken at a depth of 45 or 50 cm. Furthermore, these samples were totally different in physical character, being of a lighter color, often water-white,

and containing lesser amounts of starch. . . . Very little difference was found between fractions obtained at 45 and 50 cm., respectively. However, the fact that these two fractions are usually in close agreement indicates that in that region the stomach contents were, perhaps, of a more homogeneous character. In plotting the curves of fractions taken at each level, a certain general similarity may be noted, despite the recrossing at numerous points. This might seem to indicate that if the level of the tube were kept constant, single determinations might yield a characteristic curve. However, the errors are too fundamental to be thus lightly disregarded." In conclusion he states: "Aliquot fractions obtained by the Rehfuess method of gastric analysis cannot be assumed to represent accurately the total gastric contents."

White states: "Fractional analysis is based, either consciously or unconsciously, on the assumption that small fractions of the gastric contents represent the whole content of the stomach at the time, and that fractional curves, as ordinarily obtained, represent changes in gastric secretion." He then studied 50 cases by the method of rapid divided extractions, and demonstrated a marked variation in the acidity of the different samples. He summarizes in part as follows: "Fractional analysis is only a rough method of testing gastric secretion. Accidental variation may amount to 50 or 100 per cent of the figures obtained. Only gross changes in acid have clinical importance. The recognition of these limitations seems likely to lessen its use in the future."

Friedenwald agrees that the gastric contents is not a homogeneous mixture, and concludes that: "(1) Stomach contents are not homogeneous as evidenced by variations in fractions aspirated in rapid succession and by changing the position of the tip; (2) the tip resting in the pars media and pylorica gives fairly accurate information regarding gastric digestion; (3) variations may be reduced by mixing the contents of the stomach; (4) daily variations in acidity of gastric contents occurs, but this variation is moderate—a hyperacid, normal or hypoacid secretion continues as a rule to present the same character of acidity."

It is apparent from the above that all these authors are in general agreement as to the following points: They accept the statement of Gorham that "The fractional method of gastric analysis is presumably based on the assumption that the gastric chyme after a test-meal is a homogeneous mixture." They are all able to prove that the gastric contents is not a homogeneous mixture, therefore they either question the value or frankly condemn the fractional method of gastric analysis. Kopeloff came closest to the real purpose of fractional gastric analysis when he showed that curves obtained simultaneously from different parts of the stomach had the same general character, but that the physical characteristics of the material withdrawn showed marked differ-

ences. However, he seems to have disregarded these findings in his conclusions and to be in agreement with the other authors cited.

These criticisms, I firmly believe, are not justified, and tend to shake the confidence of the profession at large in a clinical procedure of great value in the proper study of the gastro-intestinal tract. In the first place, after a careful review of the literature I can find no statement by any advocate of the fractional method, that the samples extracted are representative of the whole stomach contents, and therefore it seems to me that the "presumption of the assumption" on the part of Gorham is unwarranted. In the second place, any variation in the acid values of different parts of the stomach is based on the physiology of the organ, and the proof of such variation cannot be used as argument against a method admitting such variation. A short recapitulation of the fundamental principles, purposes and limitations of fractional analysis and a review of the anatomy and physiology of the stomach may not be out of place and will serve as a foundation for the subsequent development of the subject.

As I have just said, fractional analysis is not based on the assumption that the samples extracted are representative of the whole stomach contents at that time. It is not primarily interested with the stomach contents as a whole at any one time but rather in studying, by sample extractions from the proper point, the result of the action of the stomach on the food material introduced. As has been repeatedly emphasized, especially by Rehfuess and Hawk,⁶ fractional analysis is a measure of gastric work, and for the sake of convenience the sum total of gastric work may be divided into different periods and factors. The first period is the interdigestive phase, represented by the fasting stomach. As the stomach is never entirely idle this represents the base line of secretory and motor activity, and it also affords the opportunity to study any additions to the stomach contents from above or below since these additions are then present in their greatest concentration and are not obscured by the material undergoing digestion. During the second period, the digestive phase, the gastric work may be considered in three general divisions: The first of these, and relatively the least important, is the secretory response as determined by the amount of gastric juice added to the digestion mixture; the second is the amount of comminution of the material serving as the test load and its mixture with the gastric juice; the third factor is the rapidity with which the stomach passes on the test load or, in other words, the motor end point. While all these factors are interrelated to a certain extent, still anyone of them may vary independently of the others, and it is only by studying all of them that a true estimate can be obtained of the response of the stomach to the test load. As was previously pointed out,⁷ fractional analysis is not a simple procedure, and any technic that

does not take into consideration all of the above factors does not return the greatest possible amount of information. As fractional analysis is only to be considered as a measure of gastric work expressed in the three factors of secretory response, mechanical division and mixing and motor end point, only those pathological processes which alter one or more of these factors are susceptible of demonstration by this method. We cannot hope to demonstrate changes in form, position, contour or mobility.

The findings of the anatomist and physiologist regarding the stomach that have a direct bearing on the question of fractional gastric analysis are as follows: Embryologically the stomach is a straight tube surrounded by circular bundles of muscle fibers, and it is by bending and a ballooning-out of one side of this tube that the adult form of the stomach is gradually produced. During fetal development there is a quite distinct division of the stomach into different parts suggesting the condition found in the compound stomach of ruminants.⁸ The fixed points of the stomach are the cardiac and pyloric ends, and, whereas the distance between these points along the lesser curvature maintains a definite relation to the size of the growing individual, the increased capacity of the stomach is obtained by a distention of the greater curvature. In the arrangement of the oblique muscle fibers there is a mechanism for reducing the size of the fundus, for the lines of force exerted by the contraction of these bundles, aided by the circular fibers, would tend to restore the organ to its original tubular form.

There is also a difference in the histology of the mucosa of the different ends of the stomach, and Radaseh⁹ has shown that the transition from one to the other is quite sharp, especially as regards the acid cells. This anatomical arrangement would suggest that even in the adult human stomach there is a division into two definite parts, and this conclusion is further supported by a consideration of the physiology of the cardiac and pyloric ends of the organ. Alvarez¹⁰ has demonstrated graded differences in rhythmicity, irritability, tone and latent period between the muscle of different parts of the stomach. Roentgen-ray observers have noted that during the height of digestion peristaltic waves may be seen originating high in the fundic portion and progressing as shallow indentations, pass over the organ until a point is reached, at a fairly definite distance from the pylorus, where each wave changes its character, deeply indenting the outline of the stomach and at times completely obliterating the lumen. It has long been known that the acid of the gastric juice was formed in the fundus, and Ivy and Oyama¹¹ have recently shown that the secretion of the pyloric part is definitely alkaline. Thus anatomy and physiology both point to the fact that the stomach cannot be considered as a whole but rather as an organ with two distinct parts differing in form, structure and function. The fundus serves as a reservoir or hopper for

the rapid reception of large amounts of food. Here salivary digestion continues in the interior of the mass while the outer layer, composed of the food first ingested, is subject to the action of the gastric juice. Aided by the gentle pressure exerted by the fundus, which pressure nicely adjusts itself to the amount of food present, the softened outer layers of the mass are gently stroked toward the pylorus. Here the semifluid material is kneaded by the vigorous peristaltic waves passing over the antrum until the individual masses have become finely comminuted and the whole intimately mixed with the gastric juice. At this point the pylorus opens and the chyme is ejected into the duodenum. Alvarez says "It is now well known that there are three parts of the stomach: (1) The fundus, which holds the food fairly motionless, often in layers, as it comes in; (2) the muscular antrum, which breaks the food up and mixes it with the gastric juice; (3) the *canalis gastricus*, which carries fluid along the lesser curvature and out into the duodenum."

With this conception of fractional analysis and the physiology of the stomach, the present investigation was undertaken, the object being to demonstrate if possible the following points:

1. That, although differing in acid values, if a constant relation be maintained between the points of extraction, fractional curves from different parts of the stomach would not cross but be similar.
2. To show the difference in the physical properties of samples from different parts of the stomach.
3. To show that extractions from the antrum give the most information as to the work being done by the stomach.

Technic. The apparatus used was modified from that of Epstein¹² and consisted of two standard duodenal tubes with Lyon tips. One tip was grooved along its lateral surface, so as to receive the tube passing to the more distal tip. In order that the two tips should maintain a definite relation to each other, the grooved tip and tube were lashed to the other tube in such a position that the tips were 10 cm. apart.

The patients presented themselves six hours after a test-breakfast and the double tube was passed. No serious difficulty was encountered, although in most instances this represented the patient's first experience with gastric intubation. The amount of the tube to be introduced in each case was roughly estimated by placing the upper or grooved tip at the xyphoid and measuring on the tube the distance to the patient's upraised chin. Introducing the double tube to this distance was found to bring the lower tip well into the antrum, with the upper tip in the fundus along the lesser curvature. With this arrangement the tips maintained a constant relationship to each other, and varied as little as possible their relative position in the stomach, as it was shown that the lesser curvature was the least subject to change in length and position during the process of digestion.

With the tube in position, as much of the fasting content as possible was extracted through the upper tip, and the stomach was then completely emptied through the lower tip. In this way not only the differences in acidity but also the differences in physical properties and amount of material in the two parts could be noted. The standard Ewald meal was then eaten with the tubes *in situ*. Extractions were made at half-hour intervals simultaneously from both tubes, and the notes and titrations recorded at once. Great care was taken to free the tube of its contents after each extraction by injecting air, but this was done with caution so that the tube was just emptied and little or no air escaped from the tip, for if any large amount were injected it would tend to disturb the digestion mixture as it ascended into the fundus. At the two-hour period as much material as possible was extracted through the upper tip and immediately following this the stomach was completely emptied through the lower tip. A test-lavage was then given with plain water, which was run in through the upper tip and siphoned off through the lower tip. In this way it was made certain that the stomach was entirely empty. During the entire procedure the patients were instructed to expectorate all saliva into a receptacle.

Discussion. The charts presented herewith are representative of the results of double gastric analysis as outlined above. The patients were all attending a gastrointestinal clinic and, therefore, none of the series can be taken as normal. However, as no attempt was being made to fix the normal, more information was to be expected from patients with gastrointestinal complaints.

In regard to the information obtained bearing on the original points of investigation, I think that the demonstration is conclusive. The first object of this investigation was an endeavor to show that fractional curves from different parts of the stomach would be similar. Chart I is typical of the results obtained when the curves were uninfluenced by biliary regurgitation. It will be seen that the acidity of extractions from the fundus and the antrum form entirely similar curves differing only in acid value. This similarity was also demonstrated in cases of achylia and hyperacidity, but space does not permit the presentation of these charts. A point of interest is that, although the hydrochloric acid is secreted in the fundus the highest acid values were found in the antrum. I believe that the answer to this point lies in a difference in concentration, or rather dilution, of the acid as secreted, but further work will have to be done on the point. It will also be noticed that, with the bread and water meal, there is a tendency for the contents of the two parts of the stomach to have the same acid values during the second hour, except in those cases in which the acidity continues to mount during the second hour. This finding is probably due to the diffusion of the acid through the rather fluid

meal, and in the usual mixed meal of the normal diet would not occur to such a marked degree.

As is noted on Chart I, *B* and *C* on the line marked chyme stand for bread and chyme. In those marked *B* the extraction contained small crumbs of bread in water and on straining through gauze or cotton the filtrate is water-clear. In those marked *C* the material extracted is thicker, homogeneous or finely granular, creamy in color and even on straining the filtrate is a little turbid. It must be assumed that this change in the character of the extractions is due to the peristaltic activity of the antrum, and represents the comminution of the test-substance and its mixing with the gastric juice. This is part of the work of digestion done by the stomach, and the performance of this work can be followed through the fractional gastric analysis. In all the charts it will be seen that the extraction from the fundus contained bread crumbs, and that from the antrum contained chyme.

From an examination of all the charts it can be seen that, except in those with biliary regurgitation, all the factors of gastric work can best be followed by extractions through the tip in the antrum. Even in those cases with biliary regurgitation, although a true picture of the gastric acidity may not be obtained, the important fact of the presence of biliary regurgitation would be missed unless the tip were in the antrum. The ideal place to study gastric work would be the first part of the duodenum, providing regurgitation from beyond could be effectually blocked. As this is not routinely practical we must be content with the extractions through the tip in the antrum.

This work is in entire accord with that of Lockwood and Jacobson,¹³ who say "Obviously the acidity of any one portion extracted through the small tube depends on the location of the tip of the tube and gives the character of the contents of that part at the time. Just as obvious is the assumption that if the tube stays in the same place one could, by extracting at definite intervals, obtain the cycle of events through a long period. This we believe is what happens and the reason one gets such beautiful curves in the majority of cases. Any marked sudden deviation of the curve can be explained by a change in the position of the tip, or by duodenal regurgitation. The chief cycle of stomach chemistry takes place in the pars media and pars pylorica which are the lowest parts of the organ. If the tube is of sufficient weight to sink in the stomach contents, and if the patient remains in the sitting position or if reclining remains supine, these conditions are in the majority of cases fulfilled and a steady curve is obtained. Repeated roentgen-ray observations have convinced us that the tube tip, due to gravity and peristalsis, generally rests near the outlet of the stomach, therefore the fractional method with proper technic represents the cycle at that most important portion of the stomach,

allowing one to observe the acidity, presence of pathological products, duodenal regurgitation and the presence or absence of food."

On examining these charts there are several other points besides those already mentioned that are of considerable interest. Chief among these is the question of biliary regurgitation. Entirely aside from whether biliary regurgitation is normal or not, these charts present the subject from a somewhat different angle. All the charts presented, with the exception of Chart I show biliary regurgitation in one or more of the fractional extractions, and the most striking thing about the regurgitation is that it appears only in the extractions from the antrum. In no instance was bile

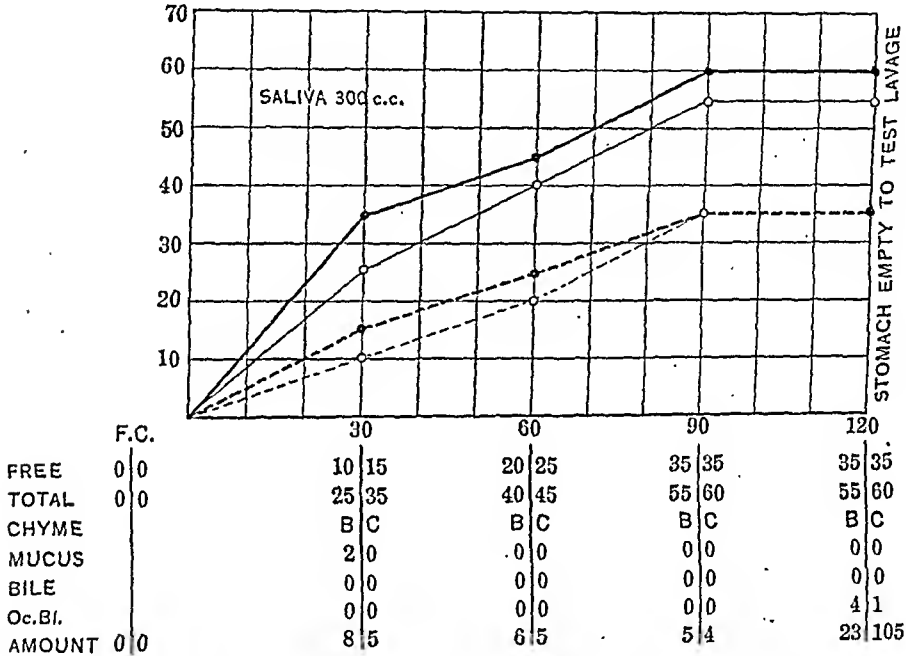


CHART I.—In this and subsequent charts solid lines denote total acidity and broken lines free hydrochloric acid. Heavy lines are extractions from the fundus; light lines are from the antrum. Notes in left hand column refer to fundus; those on right to extractions from the antrum. Scale 0, 1, 2, 3, 4, Amounts in cc. Note similarity of curves.

present on inspection in any of the samples taken from the fundus, although it was present at the same moment in the antrum in concentrations ranging from a faint yellow tinge to a deep yellow. The most generally accepted theory as to the purpose of biliary regurgitation is that it is a mechanism of the intestinal tract to overcome the supposedly high acid values existing at that time in the stomach. From an analysis of these charts that theory seems hardly acceptable since it is shown that the regurgitated bile never reaches the fundus of the stomach where, during most of the digestion period, the large mass of food is held. But of even greater interest than the fact that the entire stomach contents is not affected by the regurgitation of bile is the fact that, while

there is biliary regurgitation into the antrum with a consequent lowering of the acidity, the acidity of the fundus may continue to rise and even reach considerable heights (Charts III and IV). That biliary regurgitation is not necessarily associated with high acid concentration is shown in Chart II, where the acidity of the fundus is only 20 free and 40 total, and yet there is biliary regurgitation Scale 3. Up to the present the very fact of the finding of biliary regurgitation presupposed a hyperacidity, for, no matter what the acidity of the sample containing the bile, it was presumed to have been cut to that point from an abnormally high acidity. The taking of simultaneous extractions from the fundus has shown that biliary regurgitation occurs in cases with low original acidity. Another phase of biliary regurgitation that these charts throw some

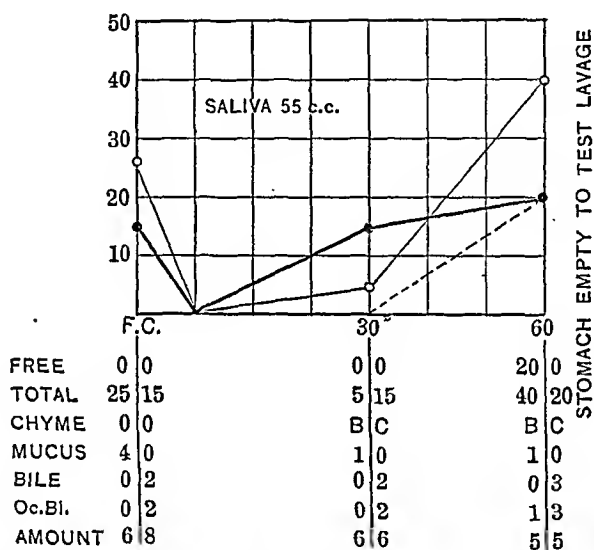


CHART II.—Crossing of curves for total acidity is due to biliary regurgitation into the antrum. This was sufficient to entirely neutralize the free hydrochloric acid in the specimen at sixty minutes.

light on is the question of exactly how much biliary regurgitation is capable of cutting the acidity of the gastric juice. Charts II and IV of this series throw most light on this question. In Chart II it will be seen that a Scale 3 regurgitation at sixty minutes' cut the acidity of the antrum to 0 free and 20 total, while the simultaneous extraction from the fundus showed values of 20 free and 40 total. This is a cut of at least 50 per cent in the total acid and a complete neutralization of the free acidity. In Chart IV a Scale 4 regurgitation at one hundred and twenty minutes caused a cut from 85 free and 110 total in the fundus to 25 free and 55 total in the antrum. This is a really surprising reduction and yet represents a cut of only 50 per cent in the total acidity.

These findings strengthen the conclusion that biliary regurgitation is not primarily caused by high acid concentrations in the

stomach. If we cannot find the cause of reverse peristalsis in changes in the contents of the digestive tract then we must look for the cause in the changes in the muscular wall of the tube. The normal direction of flow of the contents is aboral, and Alvarez has explained the mechanism of this in the gradient idea. Reversal of flow has been repeatedly demonstrated, and in several locations has even been considered physiological by certain investigators. It has also been demonstrated that any irritative lesion affecting the musculature of the digestive tube increases the degree and frequency of reverse peristalsis, especially in portions of the diges-

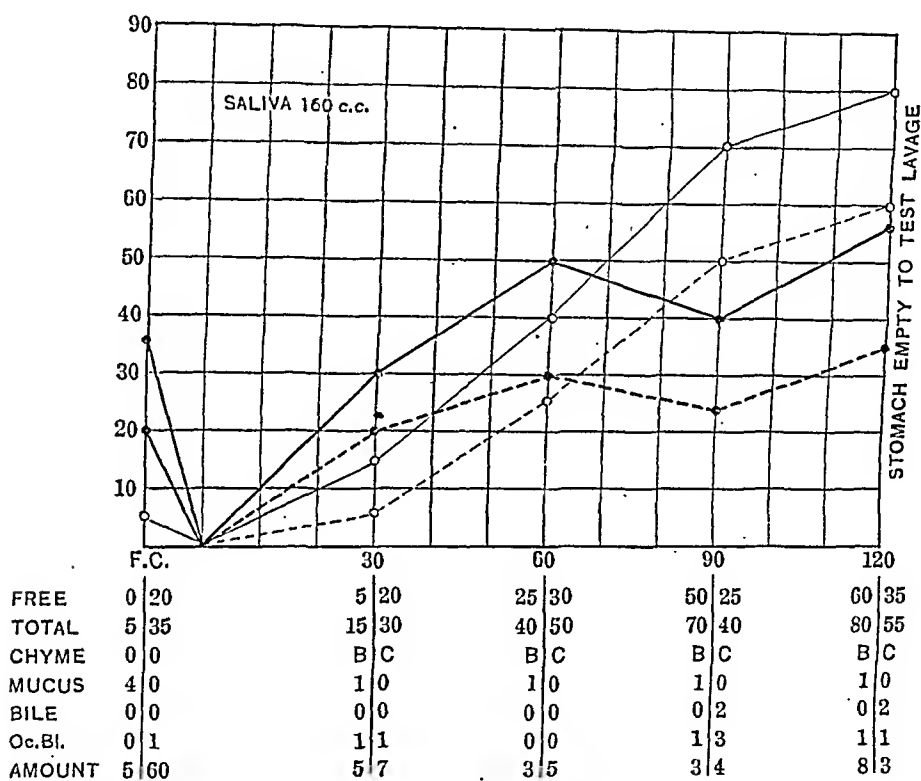


CHART III.—Crossing of curves for both total acidity and free hydrochloric acid due to biliary regurgitation. Acidity in fundus continues to ascend.

tive tube above the lesion. It seems more plausible then to assume that biliary regurgitation, especially during digestion when the flow of contents in the canal should be most definitely and continuously aboral, is to be considered as evidence of an irritative lesion disturbing the normal gradient, the lesion in all probability being distal to the pylorus.

Another point that is brought out by these charts is that the tip of the tube must remain in the same position throughout the test if the information obtained is to be accurate. If during the course of a fractional analysis the tube should slip in or out, it must be returned to its original level before the next extraction is made.

Likewise if there is any difficulty in making any of the extractions it is not permissible to pull the tip out a little way or to inject air in any quantity to free the tip. These procedures will either change the position of the tip in the stomach or so disturb the digestion mixture that the acid value of the sample so obtained will not represent a direct continuation of the curve built up from the previous extractions.

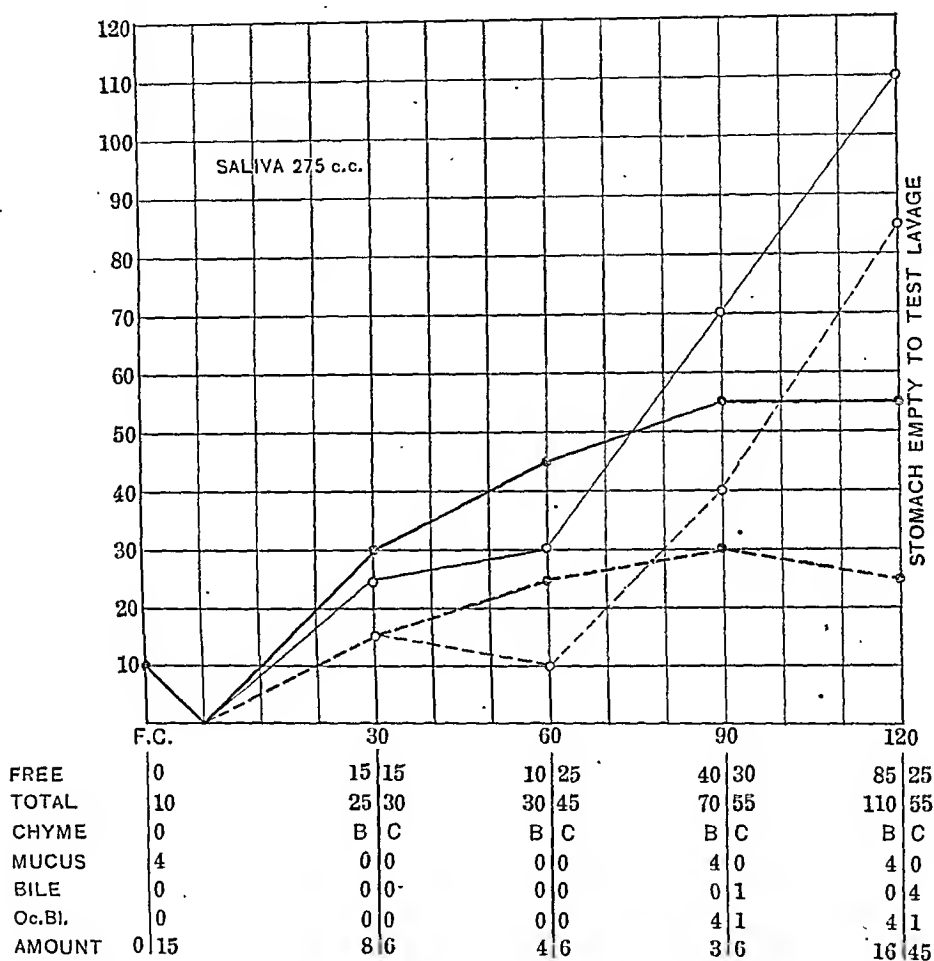


CHART IV.—Crossing of curves due to biliary regurgitation. At one hundred and twenty minutes this is sufficient to cut the acidity of the fundus in half.

Summary. 1. Simultaneous fractional gastric analysis from two points in the stomach definitely fixed 10 cm. apart produce curves that are entirely similar in their general characteristics except where influenced by biliary regurgitation. The acid values from the antrum are always higher than those from the fundus except where the former are cut by biliary regurgitation. With the bread and water meal there is a tendency for the acid values of the two parts to become equal during the second hour due to the diffusion of the acid through the fluid meal.

2. There is a recognizable difference in the physical properties of the extractions from the fundus and the antrum, this change being due to the comminution of the test substance by the peristaltic activity of the antrum. If this comminution is not found in extractions from the antrum it is evidence that the stomach is not doing a portion of the work it normally should do.

3. The antrum, close to the pylorus, is the best place to study gastric function for there the stomach has most nearly completed its work on the test material and the condition, both physical and chemical, in which the test material will be passed on to the duodenum can best be determined.

4. Fractional analysis when properly performed is of great assistance in the clinical determination of the capacity of the stomach for work under test conditions. It must be firmly kept in mind, however, that the "fractional" feature of the examination does not refer to the contents of the stomach but rather to the work being done by it. It is only by frequent sample extractions of the result of gastric work that we can form any true conception of the course and completeness of gastric digestion.

5. Biliary regurgitation does not pass beyond the antrum into the fundus and therefore its neutralizing effect does not extend to the large mass of food held there, the acidity of which may continue to rise.

6. Biliary regurgitation cannot be considered primarily as a mechanism to neutralize a high gastric acidity: (1) Because its influence does not extend to the whole stomach contents, and (2) because it does occur in the presence of an original low acidity. It seems more probable that biliary regurgitation is an expression of the reverse peristalsis caused by a lesion either directly or indirectly irritating the muscular wall of the intestinal tract.

7. Any change in the position of the tip of the tube during the course of the test alters the curve and defeats the object of the fractional type of analysis.

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THE COMPARATIVE VALUE OF BLOOD TRANSFUSION AND BLOOD TONICS IN SECONDARY ANEMIAS.*

BY MARTIN LEWIS JANES, M.D.,

NEW YORK.

(From the Surgical Service of Dr. Charles Gordon Heyd, New York Post-Graduate Medical School and Hospital.)

THERE are several reasons for the widespread use of blood transfusion of recent years: (1) The just recognition of the procedure as an effective therapeutic measure. (2) The observation made by Landsteiner, in 1900, of the phenomenon of iso-agglutination and the practical elaboration of that phenomenon by Jansky and later Moss; the proper grouping and testing of the blood of the donor with that of the recipient has eliminated the alarming reactions following blood transfusion, which sometimes proved fatal. (3) The surmounting of the mechanical difficulties incidental to blood transfusion through the revival of the von Ziemssen syringe method in this country by Lindeman and the recent improvements in technic, one of which I have described,¹ in which the syringe is employed.

Phenomena of Red Cell Regeneration. The recent investigations of Drinker, Drinker and Lund² on the circulation of the blood in bone marrow, have shed some light on the phenomena which are instrumental for the appearance of the red cells in the blood stream. They have observed that the delivery of the red blood cells to the blood stream, in the absence of bone-marrow disintegration, is controlled by the growth pressure of the developing erythrocytes. The stimulus which is responsible for the proliferation of the red cells also causes the passage of these cells through the delicate walls of the marrow capillaries. The relative fall in pressure level between the red cell forming areas and the adjacent capillaries on the one hand and the areas of developing erythrocytes and

* Read before the Eastern Medical Society of the City of New York, March 14, 1924.

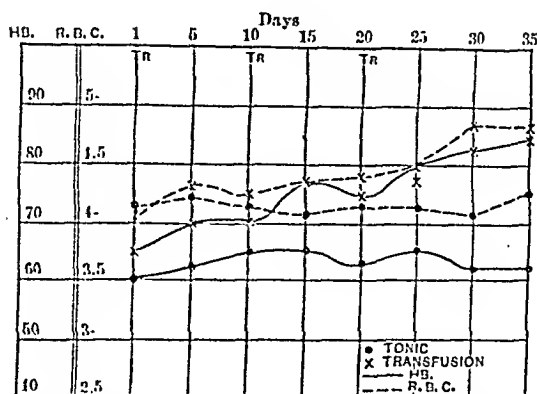


FIG. 1.—Graphic chart showing comparative results with blood tonic and blood transfusion. Patient F. R. F. Furunculosis. Fowler's solution M. 5. Tr.—Transfusion days.

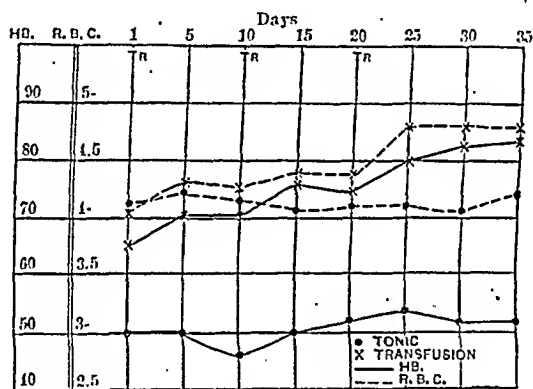


FIG. 2.—Patient J. J. R. Chronic gonorrheal arthritis. Caccodylate of iron.

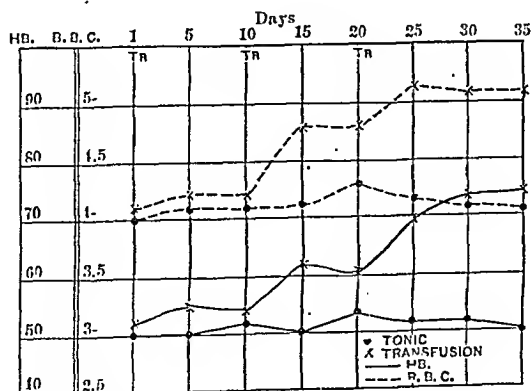


FIG. 3.—Patient J. McG. Chronic osteomyelitis tibia. Bland's pills.

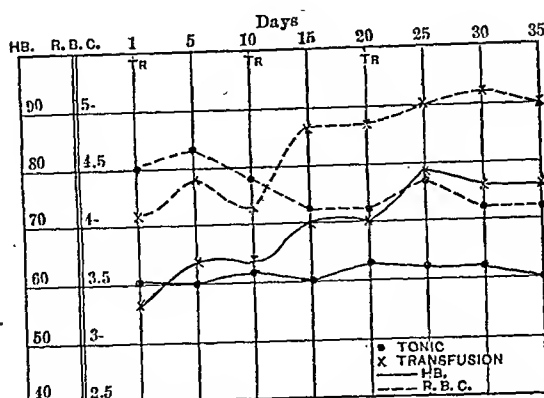


FIG. 4.—Patient H. H. Chronic nephritis. Basham's mixture.

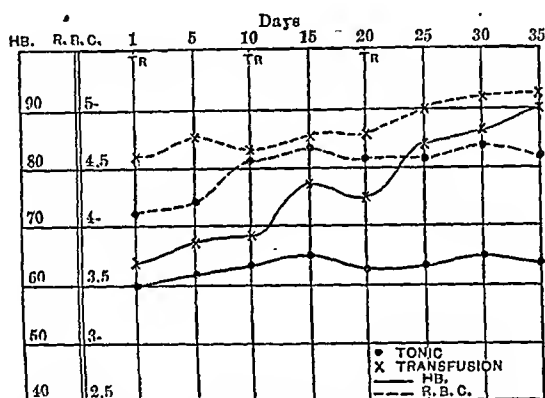


FIG. 5.—Patient R. F. Convalescing lobar pneumonia. Ferrous iodide.

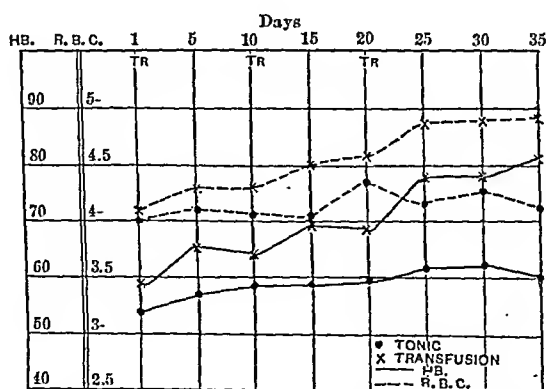


FIG. 6.—Graphic chart showing comparative average results obtained from administration of inorganic iron and arsenic preparations and blood transfusion in the 10 cases studied.

surrounding marrow on the other is the determining factor for the delivery of red cells following bone marrow stimulation. Thus, after a single large hemorrhage immature red corpuscles appear in the circulation as soon as the growth pressure of the stimulated erythropoietic areas exceeds the pressure of the surrounding bone marrow, but it is possible that after repeated hemorrhage a stage of adjustment may be reached where the immature forms do not appear in the blood following further hemorrhage. Therefore, absence of immature erythrocytes in the circulating blood does not mean necessarily an inactive or hypoplastic marrow.

Life of the Red Blood Cell. The experiments of Ashby,³ based on the transfusing cells of Group IV into individuals of unlike group and observing the time that elapses until the disappearance of the transfused cells, have shown that the length of life of a transfused corpuscle in a normal individual is about thirty-nine days.

The Role of Iron in Animal Life. Iron has long been recognized as one of the essential constituents of both plant and animal life. In the animal body the chief function of iron is to supply and maintain the hemoglobin of the blood. Hemoglobin is an organic iron compound, peculiar to animal life, which possesses a special chemical property by means of which it is able to absorb and condense oxygen.

The twenty-five million millions of red blood cells floating in the blood of a man of average size have a combined area of about 22,000 square feet or about $\frac{1}{2}$ acre.

The life of the red blood cell being only about six weeks, of the total number of red blood cells 7,000,000 die every second of our lives, and in order to keep the number normal and constant an equal number must be created by the blood-forming organs of the body every second, which is a striking example of the remarkably intense activity of those organs and of their essential importance for the maintenance of the normal balance.

The body of a man weighing 150 pounds contains 1 part of iron to 24,000 parts of body weight. The blood, constituting 7 per cent of the body weight, contains about 95 per cent of the iron, in the form of hemoglobin. When one considers that the entire body normally contains but 44 gr. of iron, the wisdom of administering 5 to 15 gr. of iron daily becomes questionable. One cannot help but be amazed at the marvelous efficiency of but a few grains of iron in entrapping the life-giving oxygen and circulating it throughout the body to every cell and bringing it in immediate contact with the most minute waste particles, and carrying back to the lungs the products of combustion in the form of carbon dioxide, by far the most bulky and most important of our excretions, amounting to more than forty times the weight of urea eliminated and 400 times the weight of uric acid excreted.

TABLE I.—TONIC ADMINISTRATION.

Patient.	Age.	Sex.	Cause of anemia.	Drug.	Hb.—Days.								R.B. C.—Days.							
					1	5	10	15	20	25	30	35	1	5	10	15	20	25	30	35
F. R. F.	26	M.	Furunculosis	Fowler's	60	63	65	65	63	65	62	62	4.1	4.3	4.2	4.1	4.2	4.2	4.1	4.3
J. J. R.	21	M.	Chronic gonorrheal arthritis	Cacodylate of iron	50	50	46	50	52	54	52	52	3.8	3.6	3.6	3.8	3.8	4—	4.1	4—
H. L. F.	30	M.	Asthenia	Cacodylate of iron	46	50	54	60	66	70	78	74	3.4	3.6	3.9	4.2	4.6	4.6	4.8	4.6
J. L.	42	M.	Chronic rheumatic arthritis	Blaud's pills	54	56	54	50	52	56	56	54	3.8	3.8	3.6	3.6	3.8	4—	4—	4.1
L. R.	38	F.	Sciatica	Ferrous iodide	68	68	70	66	70	72	74	70	4.1	4.2	4.2	4—	4.2	4.4	4.5	4.4
J. McG.	44	M.	Chronic osteomyelitis	Blaud's pills	50	50	52	50	54	52	52	50	4—	4.1	4.1	4.2	4.4	4.2	4.2	4.1
H. H.	36	M.	Chronic nephritis	Basham's mixture	60	60	62	60	64	62	62	60	4.5	4.7	4.4	4.2	4.2	4.4	4.2	4.2
L. V. S.	32	M.	Chronic bronchitis	Citrate of iron	56	58	58	60	62	64	68	66	4—	4.2	4.3	4.4	4.2	4.1	4.2	4.3
R. F.	24	F.	Convalescing lobar pneumonia	Ferrous iodide	60	62	64	66	64	66	66	64	4.2	4.4	4.6	4.8	4.6	4.6	4.8	4.6
S. F.	46	F.	Chronic nephritis	Basham's mixture	52	52	54	52	50	52	50	50	4.1	4.2	4.1	4.3	4.1	4.2	4.2	4.1

TABLE II.—BLOOD TRANSFUSIONS AT TEN-DAY INTERVALS.

Patient.	Age.	Sex.	Cause of anemia.	Treatment*	Hb.—Days.								R. B. C.—Days.															
					Tr.		Tr.		Tr.		Tr.		1		5		10		15		20		25		30		35	
					1	5	10	15	20	25	30	35	1	5	10	15	20	25	30	35								
F. R. F.	26	M.	Tuberculosis	65	70	70	78	74	80	82	83	83	4.1	4.3	4.2	4.4	4.4	4.4	4.8	4.8	4.8	4.8	4.7				
J. J. R.	21	M.	Gonorrheal arthritis	54	58	58	64	64	72	70	70	70	4—	4.4	4.2	4.6	4.6	4.4	4.8	4.8	4.6	4.6					
H. L. F.	30	M.	Asthemia	66	74	72	78	76	86	94	92	92	4.6	4.8	4.8	4.6	4.2	5—	5.2	5.2	5.2	5.2					
J. L.	42	M.	Chronic rheumatic arthritis	54	58	64	62	64	70	68	76	76	3.8	4—	3.8	4.2	4.2	4.2	4.6	4.4	4.4	4.4					
L. R.	38	F.	Sciatica	70	78	76	84	84	88	90	92	92	3.8	4.2	4.2	4.6	4.6	4.8	5.2	5.2	5.1	5.1					
J. McG.	44	M.	Chronic osteomyelitis	52	56	54	62	60	70	72	74	74	4.2	4.4	4.4	4.8	4.8	4.8	5.2	5.2	5.2	5.1					
H. H.	36	M.	Chronic nephritis	58	64	62	70	70	78	76	76	76	4.1	4.4	4.2	4.8	4.8	4.8	5—	5.1	5—	5—					
L. V. S.	32	M.	Chronic bronchitis	62	66	62	70	68	76	76	82	82	4—	4.2	4.2	4.6	4.6	4.8	4.8	4.8	5—	5.1					
R. F.	24	F.	Convalescing lobar pneumonia	64	68	68	78	76	84	86	90	90	4.6	4.8	4.6	4.8	4.8	4.8	5—	5.1	5.1	5.2					
S. F.	46	F.	Chronic nephritis	50	54	50	58	56	66	70	74	74	4—	4.1	4.2	4.4	4.4	4.2	4.6	4.6	4.6	4.8					

* Blood transfusion at ten-day intervals.

Tr. Transfusion days.

* Blood transfusion at ten-day intervals.

Tr. Transfusion days.

TABLE III.—COMPARATIVE RESULTS WITH BLOOD TONICS AND BLOOD TRANSFUSIONS.

				Hb.—Days.										R. B. C.—Days.																						
Patient.	Age.	Sex.	Cause of naemia.	Treatment.	1		5		10		15		20		25		30		35		1		5		10		15		20		25		30		35	
					To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr
F. R. F.	26	M.	Furuncu- losis	Fowler's	60	65	63	70	65	70	65	78	63	74	65	80	62	82	64	83	4.1	4.1	4.3	4.3	4.2	4.2	4.1	4.4	4.2	4.4	4.2	4.8	4.1	4.8	4.3	4.7
J. J. R.	21	M.	Chronic gonorrheal arthritis	Cacodylate of iron	50	54	50	58	46	58	50	64	52	64	54	72	52	70	52	70	3.8	4—	3.6	4.4	3.6	4.2	3.8	4.6	3.8	4.4	4—	4.8	4.1	4.6	4—	4.6
H. L. F.	30	M.	Asthemia	Cacodylate	46	66	50	74	54	72	60	78	66	76	70	86	78	94	74	92	3.4	4.6	3.6	4.8	3.9	4.8	4.2	4.6	4.6	5—	4.6	5.2	4.8	5.2	4.6	5.2
J. L.	42	M.	Chronic rheumatic arthritis	Blaud's pills	54	54	56	58	54	64	50	62	52	64	56	70	56	68	54	76	3.8	3.8	3.8	4—	3.6	3.8	3.6	4.2	3.8	4.2	4—	4.6	4—	4.4	4.1	4.4
L. R.	38	F.	Sciatica	Ferrous iodide	68	70	68	78	70	76	66	84	70	84	72	88	74	90	70	92	4.1	3.8	4.2	4.2	4.2	4.2	4—	4.6	4.2	4.8	4.4	5.2	4.5	5.1	4.4	5.1
J. McG.	44	M.	Chronic osteomye- litis	Blaud's pills	50	52	50	56	52	54	50	62	54	60	52	70	52	72	50	74	4—	4.2	4.1	4.4	4.1	4.4	4.2	4.8	4.4	4.8	4.2	5.2	4.2	5.2	4.1	5.1
H. H.	36	M.	Chronic acphritis	Basham's mixture	60	58	60	64	62	62	60	70	64	70	62	78	62	76	60	76	4.5	4.1	4.7	4.4	4.4	4.2	4.2	4.8	4.2	4.8	4.4	5—	4.2	5.1	4.2	5—
L. V. S.	32	M.	Chronic bronchitis	Citrate of iron	56	62	58	66	58	62	60	70	62	68	64	76	68	76	66	82	4—	4—	4.2	4.2	4.3	4.6	4.4	4.6	4.2	4.8	4.1	4.8	4.2	5—	4.3	5.1
R. F.	24	F.	Convales- cing lobar pneumonia	Ferrous iodide	60	64	62	68	64	68	66	78	64	76	66	84	66	86	64	90	4.2	4.6	4.4	4.8	4.6	4.6	4.8	4.8	4.8	4.6	5—	4.8	5.1	4.6	5.2	
S. F.	46	F.	Chronic nephritis	Basham's mixture	52	50	52	54	54	50	52	58	56	58	56	66	50	70	50	74	4.1	4—	4.2	4.1	4.1	4.2	4.3	4.4	4.1	4.2	4.2	4.6	4.2	4.6	4.1	4.8
Averages					55.6	59.5	56.9	64.6	57.9	63.7	57.9	70.4	60.5	69.2	61.3	77.0	62.0	78.4	60.4	30.9	4.0	4.1	4.1	4.3	4.1	4.3	4.1	4.5	4.4	4.6	4.2	4.9	4.3	4.9	4.2	4.9
Tr., Transfusions.																																			To., Tonics.	

The Negative Effect of Iron and Arsenic on Blood Regeneration. Since Menghis, in 1746, reported that he had found iron in the blood of man, the value of inorganic iron as a therapeutic agent has been both confirmed and denied by various medical men. With the abandonment, in 1906, by Abderhalden, of his contention that inorganic iron could not be converted into hemoglobin, it has been generally accepted since as a valuable therapeutic agent in combating anemia. In 1920 Whipple⁴ and his co-workers reopened the controversy by a series of publications of their studies of regeneration of the blood in anemia due to hemorrhage. In a series of papers they show that inorganic iron in the form of Bland's pills and arsenic in the form of Fowler's solution has little or no effect on blood regeneration without proper diets, and they come to the conclusion that "We may not assume, without positive proof, that inorganic iron is of value in the treatment of simple anemia."

Object of Experiment. The present series of experiments were undertaken for the purpose of determining whether the conclusion of Whipple and his co-workers holds true in secondary anemias in general, rather than those which occur after a single, large, massive hemorrhage. Another object of this experiment was to make a comparison between the effects of inorganic iron and arsenic preparations administered for a period of thirty days and repeated blood transfusion, each of 500 cc, performed by the author's method, at ten-day intervals for an equal period of time.

Method of Experimentation. Ten patients in all were studied. They were young and middle-aged individuals of both sexes, who were suffering from anemia due to either acute or chronic illness.

The patients were each given a thorough physical examination, special pains being taken to search for any signs of damage or deficiency to the blood-forming organs, and a Wassermann and complement-fixation test of the blood were performed. Complete blood counts by the usual method and hemoglobin estimation was made by the Sahli method. Hemoglobin and red blood cell counts were done at five-day intervals during the course of the treatment and charts of the findings were kept.

Since diet plays a very important role in blood and hemoglobin regeneration, they were not placed upon any special diet, but were instructed to eat the same quality and quantity of food which they usually eat.

In order to obtain the coöperation and good faith of each patient the purpose of the experiment was explained to them, and the importance of the results, not only as regards themselves, but as directly concerning humanity was emphasized to them.

The following standard drugs were employed:

Fowler's solution, 5 minims, after each meal.

Cacodylate of iron, 1 gr., three times daily after meals.

Blaud's pills, each pill containing 3 gr. of carbonate of iron, 1 pill, three times daily, after meals.

Basham's mixture, 4 dr., well diluted, after meals.

Saccharated ferrous iodide, 5 gr., three times daily, after meals.

Ammonio-citrate of iron, 10 minims, three times daily, after meals.

Findings. The accompanying tabulations of findings resulting from the administration of either of the above drugs for a period of thirty days shows an average gain in hemoglobin of 5 per cent and a gain of 200,000 in the red blood cells—an increase which is so small as to be accounted for by the human shortcomings in determining the hemoglobin or calculating the red blood cells.

Blood transfusions caused an average increase in the hemoglobin of 21 per cent and 800,000 in red blood cells, with a decided and very apparent improvement in the general physical condition of the patients.

Discussion. The observations made in this group of patients confirms the findings of Whipple⁴ and his co-workers and Musser,⁵ that iron and arsenic preparations have a negative effect on blood regeneration and the correction of anemia. The individuals selected for this experiment were taken at random, and were subjected to a careful examination for any pathological condition or deficiency in their blood-forming organs. Of course, no two individuals are alike as regards their environment, hygienic conditions, habits, recuperative powers and reactions to food, all of which are important factors for hemoglobin and red blood cell regeneration. An effort was made, however, to maintain them as nearly as possible under the same conditions both under the drug and transfusion treatment.

Summary. 1. Individuals suffering from secondary anemia due to acute or chronic disease regenerate hemoglobin and red blood cells more rapidly, more effectively, more completely and within a shorter period of time by periodic blood transfusion than those receiving inorganic iron or arsenic preparations.

2. Iron and arsenic preparations exercise practically no beneficial effect in correcting secondary anemias.

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STUDIES IN CALCIUM AND BLOOD COAGULATION. (WITH
SPECIAL REFERENCE TO THE USE OF SALTED PLASMA
AS A METHOD OF ESTIMATING CLOTTING TIME.)

BY CARL H. SMITH, M.A., M.D.,
NEW YORK CITY.

(From the Pathological Laboratory of the Lenox Hill Hospital, New York City.)

THE methods, which have been described for the determination of the clotting time of the blood, may be placed in two well-defined groups. In the first group the coagulation time of the whole blood is measured directly. The method outlined by Lee and White¹ calls for blood obtained directly from a vein and collected into a small test-tube of a definite size. Of the methods reported by Hinman and Sladen² and Solis-Cohen,³ the greater number use blood obtained by ear or finger puncture, the differences in procedure usually depending upon some specially designed receptacle, or the adoption of a novel departure in defining the coagulation point. In all of these despite the refinement of the coagulometer, lies the fundamental objection of inherent errors accompanying methods by which blood is obtained from puncture wounds. Again, no method of this group throws any light upon the individual factors involved in the process.

In the second group fall those methods in which clotting is first inhibited through the agency of some anticoagulant salt, to be restored later either by recalcification or diluting with water. Howell's method⁴ for the determination of prothrombin time, exemplifies this group inasmuch as clotting is first suspended by sodium oxalate and after centrifugalization the plasma is recalcified so that coagulation proceeds once more. In Gram's modification⁵ of this method the citrate is substituted for the oxalate. Brissaud⁶ utilizes hypertonic sodium chloride as the anticoagulant and by dilution effects a return of coagulation. With Howell's method⁴ the prothrombin factor is investigated incidental to determining the coagulation time, while this paper will consider the calcium factor in its relation to clotting.

The method employed in these studies is based on the well-known observation that hypertonic sodium chloride prevents coagulation of blood in vitro and that by dilution with water this property is restored. It is interesting to note in this connection that Velden⁷ and Schenk⁸ have observed that concentrated sodium chloride solution intravenously administered hastens blood coagulation, a marked parallelism in this respect to the action of sodium citrate as described by Weil.⁹

In his experiments on the determination of clotting time, Bris-

saud⁶ employed distilled water for the restitution of clotting in salted plasma. In adapting this method for more practical clinical use, the plan suggested itself of comparing the rate of coagulation in the salted plasma diluted with distilled water, with that in which the diluting fluid consists of water containing minute traces of calcium chloride in known concentration in order to study the influence of this salt upon coagulation time.

The Method. The blood* is collected in special test tubes graduated to 5 cc. This tube has an inside diameter of 1 cm. and a length of 7.5 cm. Similar tubes are used in the test. All of the tubes are carefully cleaned in bichromate-sulphuric acid mixture and washed thoroughly in distilled water. A pipette is constructed of glass tubing having a diameter of from 0.5 to 0.6 cm., the capillary end of which has a bore less than 1 mm. in diameter, and to the wide end a rubber nipple is attached.

A hypertonic solution of sodium chloride is prepared by dissolving 10 gm. of calcium free salt in 100 cc of distilled water. The most uniform results are obtained when this solution is from one to six weeks old. For reasons at present unknown fresher solutions prolong clotting time and older ones shorten it. Calcium chloride solutions of two strengths are used, 1 to 10,000 and 1 to 2,000 prepared by dilution of a 1 per cent stock solution of anhydrous calcium chloride.

With a sterile 10-cc syringe, blood is withdrawn by vena puncture and 4 cc are immediately placed in the graduated test tube which contains 1 cc of the 10 per cent sodium chloride solution.† The tube is closed with a paraffined cork and the contents mixed by rapid inversion. In each of 5 test tubes of the same type, previously rinsed with physiological salt solution, 1 cc of blood is placed and the coagulation time is determined by the direct method of Lee and White.¹ The salted blood is centrifuged in its container for exactly five minutes at a speed of from 1000 to 1300 revolutions. Three rows of four standard tubes each are placed in a rack, and in each tube there are placed 5 drops of the supernatant salted plasma. With the same pipette there are added to the first row, 5-6-7-8 drops of distilled water; in the second row a similar number of drops of the 1 to 10,000 calcium chloride solution and in the third the same amounts of the 1 to 2000 solution. It is essential to shake the tubes after the addition of each diluent. The final dilutions of sodium chloride in each tube therefore ranges between 1 per cent for the tube that has received 5 drops and 0.77 per cent for the one with 8 drops.

* In all cases, blood was obtained before breakfast.

† Ten per cent sodium chloride diluted to 2 per cent with 4 volumes of blood has been found superior to the 20 per cent solution reduced to 5 per cent as prescribed by Brissaud.⁶ The lower concentration of the salt while as efficient in inhibiting clotting, is more satisfactory than the stronger solution in that hemolysis is obviated.

All the tests were conducted at room temperatures, between 21 to 24° C. In order to obtain the most uniform results, it is necessary that the interval between salting the blood and the beginning of centrifugalization should not exceed ten minutes; that after the supernatant plasma is removed the test should be completed within five minutes so that the entire period elapsing from the time the blood leaves the vein until the completion of the recalcification should not exceed twenty minutes.

As set forth by Addis¹⁰ in the accurate estimation of coagulation time, the end-point must be clear and definite and always indicate the same degree of coagulation. These requisites are met with in the use of salted plasma. In the test, the time of dilution is carefully noted for each set of tubes. The latter remain undisturbed for five minutes, when the rack is raised and tilted slightly to observe the inception of clotting. This is repeated at the end of every minute thereafter, until coagulation has been completed in all the tubes, the readings being recorded as clotting takes place in the individual tube. Clotting progresses gradually through various stages of increasing turbidity and diminished fluidity to its termination. The most intense turbidity is observed in the mixtures containing the larger quantities as well as the more concentrated calcium solutions. The end-point is reached when the clot is firm and upon inverting the tube the meniscus of the coagulum remains immobile.

A protocol of a single test will serve to emphasize its salient features:

Normal Case:

	Diluting agent.		
	Distilled Water.	Calcium chlorid.	
		1 to 10,000 (coagulation time in minutes.)	1 to 2000
Five drops of salted plasma, plus			
5 drops	25	19	14
6 drops	20	14	12
7 drops	20	14	11
8 drops	15	10	8
	—	—	—
Average coagulation time .	20	14	11
Temperature, 24° C.			

In recording the results the method adopted was to note the figures comprising the average coagulation time with each diluent, in this case—twenty, fourteen, and eleven minutes respectively.

Discussion. The mechanism by which hypertonic salt solution inhibits coagulation is as yet a matter of conjecture. Lee and Vincent¹¹ offer evidence to show that concentrated solutions of sodium chloride prevent the formation of thrombin. Howell¹² states that calcium is deviated so that it cannot activate prothrombin. One is impressed constantly in studying the coagulation process that the changes involved conform to the laws of colloids and that these laws are obeyed when blood is mixed in vitro with hypertonic sodium chloride and later diluted to isotonic strength.

The inhibition of coagulation by this salt according to Pickering and Hewitt¹³ is due to the relatively stable unions of the proteins with the added electrolytes and to some extent also to the withdrawal of water. On dilution, with the reduced concentrations of the electrolytes the coagulation process once more manifests itself. The precise fate of the calcium during this process is problematical. From the observations made in the course of these studies, the only conclusions that can definitely be drawn are that upon rendering salted plasma isotonic, coagulation is restored and that with the further addition of minute traces of calcium chloride it is greatly accelerated.

It is generally accepted that calcium in common with the other inorganic bases of blood serum may exist in at least two forms: in the diffusible and potentially ionizable state and in the non-ionizable combination with serum proteins. Of the total calcium present in serum, von Meysenburg, Pappenheimer, Zucker and Murray¹⁴ found 60 to 70 per cent to be diffusible while Neuhausen and Marshall¹⁵ determined that even a smaller fraction (about 10 per cent) was present in ionizable form. In view of the incompleteness of knowledge concerning the individual roles of diffusible and ionic calcium in the coagulation of blood, the term available calcium will be substituted in contradistinction to the non-available protein-bound calcium.

A possible explanation of the action of hypertonic sodium chloride solution is that upon its admixture with blood in the concentration stated above, sufficient calcium is inactivated to aid in the suppression of clotting and that on dilution with water a considerable portion of this substance is once more brought into play in its available form. The well-known antagonism existing between sodium and calcium salts in physiological processes is pertinent at this point and has recently been described by Lillie¹⁶ in its application to fundamental biological relationships. Clowes¹⁷ extends this principle of antagonism into the province of blood coagulation since "the salts of calcium tend to promote and alkalies and salts of sodium to inhibit the reversal or transposition of phase relations of a protein sol like blood plasma into a jelly like blood clot." Novi¹⁸ refers to the "decalcifying" action of sodium chloride upon tissues. Budde and Freudenberg¹⁹ discussing the ionization of calcium in solutions containing the inorganic constituents of blood suggest that the addition of sodium chloride depresses the dissociation of calcium through the preponderance of chlorine ions.

In many respects the behavior of the citrate of sodium must be akin to that of its chloride particularly with respect to the influence of the common cation sodium. Sodium citrate according to Sabatini²⁰ inhibits coagulation not by precipitating the calcium but by checking its ionization hence rendering it unavailable for blood clotting. From this conception Bloch²¹ has evolved a theory of

coagulation based principally upon the alteration in the activity of calcium. That the evidence thus offered although largely indirect is relevant to the suspension of blood coagulation by hypertonic sodium chloride, is extremely probable but that the calcium alone is the sole factor in a process involving the interaction of so many elements requires added proof.

In rendering salted plasma isotonic with distilled water, the dissociation of calcium compounds proceeds, and available calcium is once more present for clotting. Whatever loss in concentration or activity of available calcium is sustained by salting is replaced by reinforcement with calcium chloride solutions of the two strengths designated in the procedure.

Increasing Concentrations of Calcium Chloride and the Clotting of Salted Plasma. The effect upon coagulation time of diluting salted plasma with calcium chloride solutions of increasing concentrations is illustrated in the following experiment:

Normal Case:

Average coagulation time in minutes Temperature, 22° C.	Diluting agent.					
	Distilled water.	Calcium chloride solutions.				
		1-10,000	1-2000	1-1000	1-200	1-100
	20	16	10	12	27	105

Similar observations have been reported by Heard²², who found that calcium in common with the cations of the other alkaline earths and the metals, retard clotting with the higher concentrations. The first two concentrations of calcium chloride noted in the table, were, therefore, chosen as the optimum for diluting salted plasma.

The Influence of the Interval between the Salting of Blood and its Centrifugalization upon Clotting. As stated in the discussion of the method, it was found necessary to limit the period between the collection of the blood and its salting on the one hand, and the centrifugalization of the mixture on the other to ten minutes. The necessity for this limitation was originally observed in carrying out prothrombin determinations according to the method of Howell,⁴ in which it soon became evident that as this period was prolonged, the coagulation time was proportionally shortened. Rosenthal and Baehr²³ noted like findings in studying the effect of the intravenous administration of sodium citrate upon prothrombin time. An illustration of how this influence operates with salted plasma is recorded in the following experiment:

Normal Case:

	Diluting agent.		
	Distilled water.	Calcium chloride.	
Interval between salting of blood and centrifuging.	(average coagulation time in minutes.)	1 to 10,000	1 to 2000
10 minutes	23	15	10
25 minutes	21	11	8
40 minutes	16	7	6
Temperature, 22°.			

TABLE I.—SERIES OF NORMAL CASES.

Case number.	Diluting agent.				Serum calcium.
	Distilled water. (average coagulation time in minutes.)	Calcium chloride.		Direct Coag. time.	
		1 to 10,000	1 to 2000		
1	17	11	8	8	
2	21	15	13	10	
3	17	17	12	10	
4	18	13	11	7	
5	25	13	9	10	
6	18	14	10	6	10.0
7	20	14	11	10	10.7
8	20	14	11	11	9.7
9	18	16	9	7	10.1
10	20	16	10	5	10.3
11	27	14	11	8	11.7
12	23	15	10	9	10.1
Average . . .	20	14	10	8	10.8
High	27	17	13	11	11.7
Low	17	11	8	5	9.7

Clotting of Salted Plasma in Normal Cases (Table I).—The series of normal cases comprises, in the main, minor surgical conditions in which an opportunity was afforded to observe the extent of bleeding, and where there was no reason to expect any deviation from normal coagulation time. It is apparent from Table I, that the widest variation occurs with distilled water as the diluting agent. With calcium chloride, however, the range for clotting time becomes much more limited. With the direct method of Lee and White,¹ the results of which are recorded in the table, there occasionally occur marked variations in the clotting time among the five tubes. This finding led to the use of this number of tubes for the test instead of but one as is sometimes the practice. In Table I the values for this method represent average results, the determinations for clotting time being discarded in a tube in which there was an unwarranted prolongation. Such differences are singular in view of the simplicity of the entire procedure, and the attention paid to the elimination of a number of extrinsic factors.

Clotting of Salted Plasma in Pathological Conditions. 1. *Jaundice* (Table II). The exact part that calcium plays in jaundice is as yet unsettled. King and Stewart²⁴ and King, Bigelow and Pearce²⁵ found that in experimentally produced jaundice in dogs, the calcium content of the blood was increased. This was interpreted by them as a protective mechanism against the circulatory pigments of obstructive jaundice, since combinations of calcium and the pigment proved to be less toxic than the uncombined pigment. In the 4 cases of jaundice reported by Halverson, Mohler and Bergeim,²⁶ no increase in calcium values was obtained and in 1 there was a definite decrease.

With the knowledge that jaundice is frequently accompanied by the hemorrhagic tendency, it was considered opportune to study

this condition not alone with reference to clotting time but also to the calcium and bilirubin content of the blood serum, for which new methods have recently been developed. A series of ten cases was, therefore, investigated and in these the serum calcium was determined by the method of Kramer and Tisdall,²⁷ and the icterus index by Bernhard and Maue's modification of Meulengracht's method described by Maue²⁸ and Stetten.²⁹ At the same time, clotting time was determined on the salted plasma and by the direct method of Lee and White.¹

The determinations on the salted plasma gave definitely prolonged clotting time in 6 cases, and in 5 using the direct method. With the latter a clotting time of twelve minutes or over was regarded as delayed. Case 5 showed delayed clotting with the direct method and normal time with the salted plasma, but at operation no oozing was encountered. Cases 2 and 8 gave delayed coagulation with the salted plasma, and high normal clotting time values with the direct method.

In none of the cases of this series was the serum calcium increased. In Cases 1 and 8, the serum calcium was materially reduced and coagulation prolonged. It is obvious, however, that in this group of cases, no definite parallelism exists between serum calcium content, the depth of jaundice and clotting time. In the two cases just cited with the lowest calcium values, the most intense degrees of jaundice, as measured by the icterus index, were not present. On the contrary, the highest index (Case 7) occurred in combination with a normal calcium and only a slight retardation in clotting. Again, the greatest delay in coagulation was observed in a case of obstructive jaundice (Case 6), with an index of 115 and a normal serum calcium.

Concerning the influence of the duration of jaundice upon clotting time and serum calcium, it is hazardous to venture a definite statement since the accurate onset of jaundice is subject to varied personal interpretation. Mindful of the shortcomings of this information, it is interesting, nevertheless, to note the discrepancy between the duration of jaundice and coagulation time. These findings are in accordance with those of Morawitz and Bierich,³⁰ who concluded that altered coagulation in cholemia was independent of the duration or intensity of the jaundice.

Lee and Vincent³¹ ascribe the delay in coagulation of blood in certain cases of obstructive jaundice to a lack of available calcium. In a case with a normal serum calcium and delayed coagulation, there are the possibilities that the available calcium fraction may be low or that the other factors involved in clotting of blood may be at fault.

With salted plasma, the effect of diluting with calcium chloride solutions is in general to hasten coagulation. In three instances (Cases 1, 4, 8) this acceleration was unusually pronounced and

TABLE II.—SERIES OF JAUNDICE CASES.

Case number.	History number.	Diagnosis.	Diluting agent.			Direct coagulation time.	Icterus index.	Serum calcium.	Duration of jaundice. (from onset to test)
			Distilled water. (average coagulation time in minutes.)	Calcium chloride.					
				1 to 10,000 1 to 2000 in minutes.)	1 to 2000 in minutes.)				
1 . . .	2981	Carcinoma of head of pancreas	51	28	19	12	47	8.5	Six days.
2 . . .	3505	Carcinoma of head of pancreas	34	17	12	10	75	9.2	Two and one-half months.
3 . . .	3085	Carcinoma of gall-bladder	21	15	12	8	50	11.2	Two months.
4 . . .	3833	Cholelithiasis	70*	24	15	14	110	9.7	Six months.
5 . . .	3211	Cholelithiasis	22	11	8	12	32	11.3	Two weeks.
6 . . .	5009	Cholelithiasis	0†	55*	37	25	115	10.0	Nine weeks.
7 . . .	4034	Catarrhal jaundice	30	20	13	11	140	10.0	Six days.
8 . . .	4759	Catarrhal jaundice	34†	19	13	11	100	7.4	One and one-half months.
9 . . .	4403	Catarrhal jaundice	22	15	10	8	116	9.0	Twelve days.
10 . . .	4757	Syphilis of liver	40.	32	24	15	136	10.0	Eight days.

* No coagulation in tube with 5 drops of diluting agent.

† No coagulation in tubes with 5 and 6 drops of diluting agent.

‡ No coagulation in any of the tubes.

Normal icterus index below 6.0.

probably indicates a lack of available calcium. In contrast to these, Case 6 reveals no such decided change in clotting time, findings which speak for the other elements of clotting as fibrinogen or thrombin as the factors responsible for prolonging coagulation. In this connection, therefore, the use of salted plasma as a method for estimating coagulation time may provide a means for determining preoperatively the need for available calcium and its therapeutic administration, a procedure comparable in this respect to the "calcium in vitro" test described by Lee and Vincent.³¹

2. Nephritis (Table III).

The small series of cases of nephritis from the miscellaneous group offers several features of interest. Salvesen and Linder³² have demonstrated that the decrease in serum calcium in nephritis, may be accounted for by the fall in plasma proteins which exist in combination with the non-diffusible calcium component. The values recorded in Table III, in general corroborate this decrease, save in one instance (Case 4) in which the serum calcium was even lower than a theoretical loss of the entire quota of non-diffusible calcium would warrant. This probably represents an encroachment upon the diffusible and ionizable calcium fraction. The patient in this case exhibited signs of increased excitability manifested by tremors of the face and hands, indications fundamentally of a deficiency of calcium ions. Some of the nervous disturbances of uremia, De Wesselow³³ correlates with low calcium values.

The coagulation time in these cases of nephritis does not run parallel with the serum calcium. This can be explained, however, on the basis that the decreased calcium, although representing a loss in the non-diffusible fraction, is normal at any rate with respect to its diffusible and ionizable form, in quantities sufficient at least not only to prevent the nervous symptoms, but to maintain a normal coagulation time. In the nephritics with the prolonged clotting time, there was in the one (Case 4) a probable deficiency in the available calcium, and in the other (Case 6b) a profound secondary anemia as a complicating factor. With the former the lowest calcium in the series (4.1 mg.) was obtained, and here the addition of solutions of calcium chloride to render the salted plasma isotonic produced a most marked acceleration in clotting time.

It may be assumed, then, that both the coagulation of blood and the absence of some of the nervous manifestations in nephritis are dependent upon an adequate supply of calcium ions. It remains to be seen, however, whether the calcium ions in coagulation and in the nephritic process are identical. If they are, it is possible that a marked acceleration in clotting time in a case of nephritis (Case 4), in the tubes in which calcium chloride is used to dilute the salted plasma, as compared with that using distilled water, may serve to indicate a deficiency in available calcium and a guide to the advisability of instituting calcium therapy.

TABLE III.—SERIES OF MISCELLANEOUS CASES.

Case No.	Hist. No.	Diagnosis.	Diluting agent.			Direct coag. time. (minutes.)	Serum calcium.
			Dist. water. (average)	Calcium chloride.			
				1-10,000 coagulation	1-2000 time in minutes		
1 . .	4568	Hemiplegia	11	6 3 hrs.	5 4 hrs.	7 4 hrs.	11.3
2 . .	3613	Hemophilia	0*	33 min.†	17 min.	25 min.	10.2
3 . .	4619	Pulmonary tuberculosis	32	22	14	12	8.9
4 . .	4944	Chronic nephritis; uremic twitchings 24 hours before death	43	14	14	19	4.1
5 . .	4437	Chronic nephritis; uremia; coma	21	15	8	7	7.8
6 . .	4796	Acute nephritis; three weeks later, hematuria and secondary anemia; after two transfusions, marked improvement in blood and kidney function	(a) 29	15	14	13	7.2
			(b) 32	23	19	18	7.8
7 . .	4745	Chronic nephritis; marked hemorrhage, 6 days after transfusion; 16 days after transfusion	(c) 24	22	15	13	9.0
			(a) 22	19	16	12	9.5
			(b) 23	13	9	9	8.5

* No coagulation in any of the tubes.

† No coagulation in tubes with 5 and 6 drops of diluting agent.

Summary. 1. A method for estimating coagulation time is described in which blood is salted with hypertonic sodium chloride. The coagulation time is determined after diluting the salted plasma with distilled water as well as with calcium chloride of two concentrations.

2. In carrying out this method certain restrictions must be borne in mind, such as the period elapsing between the salting of the blood and its centrifugalization, the age of the hypertonic sodium chloride solution, and the temperature at which the tests are conducted.

3. The clotting time by this method is compared with that of Lee and White in a series of normal cases, in jaundice, and in nephritis.

In the three groups the serum calcium content is also determined, together with the icterus index in jaundice.

4. It may be possible to employ this method in jaundice, as a means of determining preoperatively the effect upon clotting time of the administration of calcium, similar to the "calcium in vitro" test of Lee and Vincent.

Conclusions. 1. In the process of blood clotting, the calcium principally involved is its ionizable and available form.

2. Hypertonic sodium chloride of the strength used in the test, probably exerts an effect upon all the elements essential to coagulation and in the case of calcium resulting in its inactivation.

3. With increasing concentrations of calcium chloride in the dilution of salted plasma a gradual retardation of clotting time is observed.

4. As the period between the salting of the blood and its subsequent centrifugalization is increased, the clotting time of the salted plasma after dilution is shortened.

5. The clotting time in jaundice may be normal, but when delayed it does not run parallel with the intensity or period of duration of this condition.

6. In nephritis, a consideration of the clotting time also necessitates the differentiation between available and non-available or protein-bound calcium.

In conclusion, mention must be made of the shortcomings inherent in every method for the determination of clotting time, due to the complexity of the process. As pointed out, even so simple a method as the direct one may yield marked variations in clotting time in the several tubes employed in the test. It is impossible to state definitely the clotting time in a specified pathological condition without a large number of determinations, since individual cases present peculiar features which play a role in coagulation.

I wish to express my indebtedness to Adolph Bernhard, pathological chemist to this hospital, whose many kind suggestions and technical aid facilitated this study.

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A CLINICAL, PATHOLOGICAL AND OPERATIVE STUDY OF THE ICTERUS INDEX.

BY JOHN V. BARROW, M.D., EUGENE L. ARMSTRONG, M.D.,

AND

WILLIAM H. OLDS, M.D.,

LOS ANGELES, CALIF.

CLINICIANS are showing a markedly increased interest in the study of diagnostic methods meant to increase our knowledge of the function of the liver. Widal has attacked the problem by noting the behavior of the leukocytes after food ingestion. The normal acting liver seems to provide for a digestion leukocytosis. In certain hepatic dysfunction there is a digestive leukopenia.

More recently a number of workers¹ have utilized the behavior of bile pigments as a basis for determining the degree of liver function. Bile pigments are essentially formed from the destruction of hemoglobin, probably within the liver. However, the amount of pigment does not necessarily depend on the amount of hemoglobin destroyed. In certain cases the excreted bilirubin would undoubtedly require a complete depletion of the red cells from the serum in order to supply this excreted pigment. There must then be some additional source of pigment production. However, the liver is the most essential organ in the production of bile pigment. Hence the interpretation of the behavior of bilirubin in the blood serum

becomes the chief aim in the study of liver function. Since the destruction of hemoglobin is a continual physiological process,⁶ we must expect a certain constant of bilirubin in the normal blood serum. That normal range has been placed at approximately 1 part of bilirubin to 500,000 or 600,000 parts of serum.

When the concentration of this pigment in the blood has increased to approximately 1 part in 50,000 or 60,000 the tissue cells begin to show a visible saturation or tinging of bile and macroscopical or clinical jaundice is apparent. This range of bilirubinemia between the normal and macroscopic tinging has been termed "latent jaundice."

To determine the clinical value of the measurement of this stage is the purpose of this report.

Alice R. Bernheim³ has used the colorimeter to measure the degree of bilirubinemia in various clinical conditions, and has aptly termed this measurement the "icterus index." Following her method, the authors have carefully checked a well-studied group of cases, and have tabulated this work for further observation and study by others. Our work agrees with hers that there is a measurable and fairly constant quantity of bilirubin in the serum of the same individual normally from day to day. This serum pigment is undoubtedly quantitatively increased by such diseases as:

1. The hemolytic processes of the body, as pernicious anemia, hemolytic jaundice, hematomas, a ruptured viscus with extravasation of blood and such diseases as cardiac decompensation, pneumonia and malaria.

2. Disturbances of the biliary system, as cholecystitis, cholelithiasis, cholangitis, certain adhesions about the gall bladder and diseases of the liver involving the bile ducts.

We are in accord with Bernheim that the normal range is between 4 and 6 and that the range of "latent jaundice" lies between 6 and 15. Above 15 clinical jaundice usually begins to appear.

Van den Bergh,¹ using the Diazo reaction, attempts to work out a test that will differentiate the obstructive from the hemolytic type of jaundice. He contends that in the former condition bile is free and readily demonstrable by the test, while in the latter state the pigment is attached to certain albuminous bodies and must be liberated by means of alcohol before it can be detected. This test is only qualitative, however, and the accuracy of its differentiation has still to be carefully checked.

J. C. Friedman⁵ has reported admirably a number of cases in which he used Fouchet's test for the detection of bile pigment in the serum. While this test seems to be specific for bilirubin, it furnishes no means of measuring the intensity of the reaction. He has demonstrated that a positive test may be present during attacks of cholecystitis, and negative in the interval, which is in harmony

with the influence such attacks would have on liver function. A test, positive during a gall bladder attack, remains positive for some time after the diseased condition has subsided. We, therefore, believe we are warranted clinically to consider nearly every case of cholecystitis as an ascending infection. The resultant hyperbilirubinemia then becomes a more probable index to a disturbed liver function; by converse reasoning an encountered bilirubinemia with clinical gall bladder findings becomes a much stronger diagnostic basis for cholecystitis.

Speik, Liljedahl and Folk⁴ have recently applied Fouchet's test to a considerable group of patients. Of 40 cases, clinically and roentgenologically (and some by operative procedure) diagnosed cholecystitis, only 27 gave a positive reaction. They are at variance with practically all other observers in finding that the anemia of malnutrition—secondary in type and without other pathological findings—often has a slight increase over the normal in the bilirubin content of serum.

The primary anemias logically produce icteric sera, while those secondary in type have too low a rate of red blood cell destruction to raise the bilirubinemia to normal.

On page 586 we wish to reproduce Bernheim's chart and follow it with our own.

Previously Barrow and Franklin⁷ have pointed out the constancy, diagnostic and prognostic value of the Widal hemoclastic crisis test in typhoid fever. The icterus index runs parallel to this test in the same disease. These tests further confirm the belief that typhoid fever produces excessive biliary strain. Consequently, by their use we are able to measure a fair degree of liver function in this and other diseases. These two tests explain Ehrlich's Diazo reaction in the urine of typhoid patients. The variable degree of excretion or filtration of bilirubin through the kidneys, together with the degree of concentration in the serum, explains its value and variation as a test for typhoid fever. We know that certain cases may have a very high concentration of bile in the blood before the tissues take on the icteric tinge. It is probable that kidney excretion or filtration does not begin until this stage of tissue saturation is present. The determination of the icterus index and the "hemoclastic crisis" are relatively of very much more value in the diagnosis of typhoid fever than the Diazo reaction in the urine.

In the absence of any accountable pyogenic complication it has been generally observed that hyperbilirubinemia is accompanied by a leukopenia. It seems fair to suspect that bilirubin may have a direct relation to, or action upon, the white cell producing mechanism of the body. The leukopenia of both malaria and typhoid fever is readily explained by the presence of excess bile in the blood.

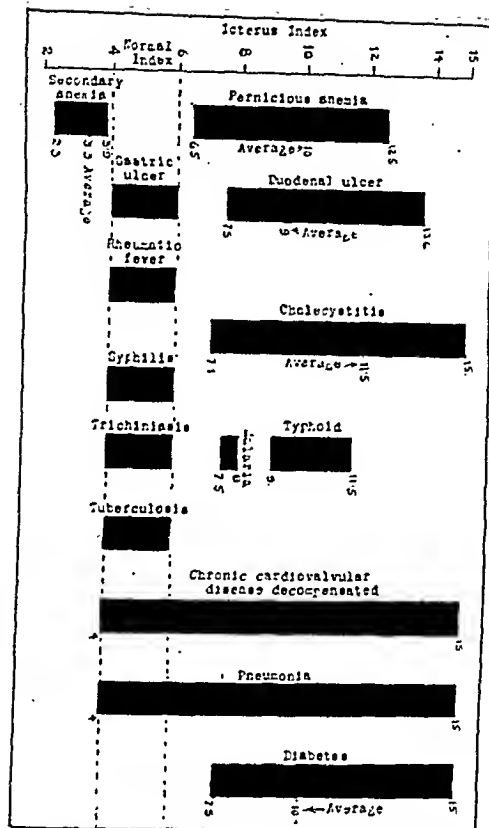


CHART I.—Icterus index in various diseases.

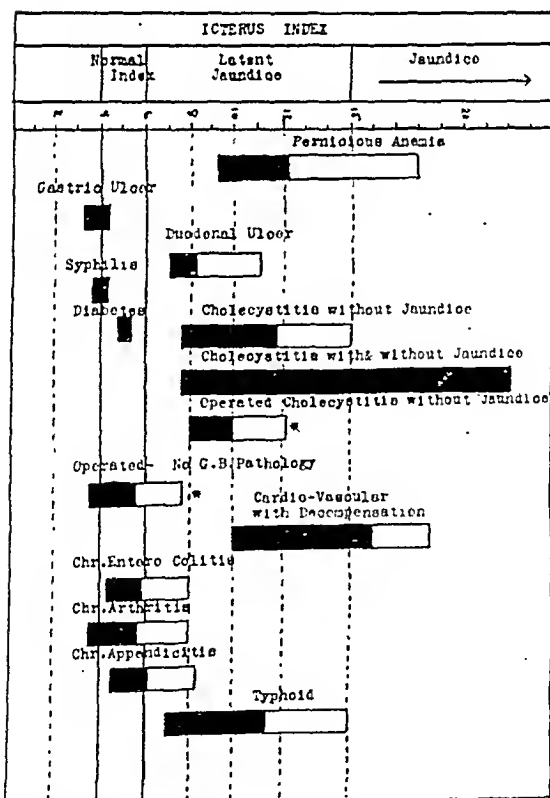


CHART II.—Solid black indicates the reading from the minimum to the average. Unfilled space indicates maximum reading of these cases. Jaundice did not necessarily occur when the reading reached fifteen. It did not occur with reading below fifteen.

Below is the tabulation of 24 cases of typhoid fever from the General Hospital service.

TABLE I.

No.	White.	Red's.	Hemo- globin.	Widal hemoclastic.	Widal.	Icterus index.
1	3150	3,100,000	70	Positive	Positive	7.0
2	3900	3,950,000	75	Positive	Negative	5.0
3	2800	3,100,000	80	Positive	Positive	9.0
4	4750	4,250,000	80	Positive	Positive	10.0
5	3500	4,150,000	85	Positive	Positive	4.5
6	4500	3,750,000	65	Positive	Positive	7.0
7	6400	4,500,000	75	Negative	Positive	5.2
8	7450	4,250,000	90	Positive	Positive	10.0
9	5400	3,100,000	80	Positive	Positive	9.0
10	8500	4,150,000	85	Positive	Positive	6.8
11	4950	3,950,000	75	Positive	Positive	8.8
12	5350	4,750,000	75	Positive	Positive	8.6
13	8250	4,350,000	85	Positive	Positive	10.0
14	5600	4,750,000	85	Negative	Positive	9.3
15	6850	4,600,000	75	Positive	Negative	10.0
16*	2700	4,050,000	70	Negative	Negative	15.0
17	5200	3,740,000	65	Positive	Positive	15.0
18	6800	4,250,000	80	Positive	Negative	10.0
19	4000	4,150,000	80	Positive	Positive	10.0
20	8050	4,250,000	85	Positive	Positive	5.0
21	5600	4,050,000	70	Negative	Positive	9.3
22	6550	3,250,000	75	Positive	Positive	7.5
23	3150	3,750,000	65	Positive	Positive	15.0
24	5300	3,950,000	80	Negative	Positive	15.0

* Case No. 16 was clinically typhoid and the typhoid bacillus was recovered from the stool by culture.

Nos. 2, 5 and 7 had the icterus index taken after intestinal hemorrhages.

The blood nitrogen in these cases was slightly above normal. The Diazo reaction of the urine cannot be averaged. The icterus index averaged nearly 12. There was no visible jaundice. The hemoclastic crisis was positive in 19 cases, or 80 per cent. The serum Widal was positive in 20 cases, or 81 per cent. The icterus index and the "hemoclastic" test are of value in diagnosis, prognosis and certain forms of treatment. Schamberg² has used the former as a guide to the administration of neoarsphenamine.

Certain of our cases presented much difficulty in differential diagnosis. The value of this test is shown by the following cases, each representing a general group:

Case Reports. CASE I.—Mrs. H. T. complained of sporadic attacks of indigestion. There had been a periodic diarrhea and alternating constipation for over a year. Certain foods distressed her but she could not tell which ones were at fault. There were frequent cramp-like pains variously ascribed to the colon, the appendix and gall bladder region. The usual cervical and back pains were present. Examination showed a low blood pressure; temperature, 99.2°; severely tender cecum; no tenderness over the gall bladder; white blood cells, 10,200; polymorphonuclears, 60 per cent; *Ameba histolytica*, spirillæ and triple plus fatty crystals

in the stool. The icterus index was 5.6. At operation a chronic appendix was found. The gall bladder was normal in every respect externally, and by its bile content and mucosa was not diseased, but it contained two unobstructing gall stones. Recovery was uneventful.

CASE II.—Mr. P. D. S. complained of blind and dizzy spells, no energy and much headache. This condition obtained for about three years. There were attacks of indigestion and extreme hyperacidity, much colon gas and a very tender epigastrium. Food did not relieve the indigestion. The bowels were fairly regular. Weight loss, 15 pounds; blood-pressure low, 100/70; temperature, 99.2°. Pain and tenderness on pressure was about equal over the gall bladder, cecum and sigmoid. White blood cells, 8200; polymorphonuclears, 56 per cent; mononuclears, 44 per cent; stools show blastocystis, chilomastix, spirillæ and fatty crystals. The stomach showed fair motility and no blood; free hydrochloric acid, 58 per cent, combined, 18 per cent, total, 76 per cent. Under treatment the patient became much better for one year, then relapsed. Icterus index before operation was 5. Operation showed a bad chronic appendix and a normal gall bladder. Convalescence uneventful and recovery splendid.

CASE III.—Mrs. R. W. L. complained of a constant and annoying pain in the right side; at times food distressed but never relieved her; soda did not help. At times there was nausea and vomiting but never any fever; severe headaches accompanied these attacks, which were worse at night. There were periodic attacks of cystitis. She never had typhoid or any serious illness before. Skin had icteric tint, but no definite jaundice. Blood-pressure, 110/80; temperature, 99°. The three points of abdominal tenderness were the gall bladder region, cecum and lower descending colon. Tenderness over the gall bladder and lower colon was about equal. White blood cells, 10,600; polymorphonuclears, 77 per cent; mononuclears, 23 per cent; stool has blastocystis and chilomastix cysts and fatty crystals; icterus index, 26.6. Diagnosis: Chronic cholecystitis and chronic enterocolitis. Operation: Gall stones removed and drainage. Appendix was normal. One week later the icterus had returned to normal. Recovery and convalescence satisfactory.

CASE IV.—Mr. N. R. M. came to the office with a severe mental depression, some nausea and extreme tiredness. During attacks of nausea the heart became very irregular and weak, and collapse was imminent. The teeth and tonsils were cared for; chest negative; upper right quadrant of abdomen only slightly rigid, but not tender. Examination showed hemoglobin, 70 per cent; red blood cells, 4,260,000; white blood cells, 6600; polymorphonuclears, 54 per cent; mononuclears, 46 per cent; stool showed Ameba histolytica, fatty crystals, chilomastix and spirillæ. Icterus index on

May 21, 1924, was 24.6. Skin showed definite icteric tinge. The diagnosis of acute cholangitis, probably amebic, was made. He was placed on rigid colon treatment, and in three weeks his symptoms were very greatly relieved. On June 21, 1924, his icterus index had returned to 6, and he has remained in good condition since.

CASE V.—Mrs. R. E. had been suffering from periodic attacks of bronchitis, with temporary smothering spells due to heart weakness. These attacks were associated with indigestion and constipation and on two occasions by a bronchial pneumonia. During her last attack the heart became very irregular and weak, with edema of the lungs and general liver engorgement. The skin was very icteric. Her blood was hemoglobin, 80 per cent; red blood cells, 4,050,000; white blood cells, 6600; polymorphonuclears, 59 per cent; mononuclears, 34 per cent; transitionals, 7 per cent. The chest showed considerable edema of the lungs, a markedly dilated right heart with very irregular weak tones. The liver was large and tender. The bowels constipated. The icterus index was 20. After rest in bed, digitalis and general treatment, the heart tones became normal and the liver reduced greatly in size. The icterus index dropped to 9.8. The roentgen-ray demonstrated a very large heart and a pathological gall bladder.

The following tables shows a small group of cases operated upon after having the test applied as an aid in diagnosis:

TABLE II.—POSITIVE FOR GALL BLADDER.

No.	Icterus index.	Roentgen-ray.	Diagnosis.	Operative findings.
7	9.5	Pathological gall bladder	Chronic cholecystitis; chronic enterocolitis	Pathological gall bladder.
8	64.0	Acute cholecystitis	Pathological gall bladder.
9	12.5	Pathological gall bladder	Chronic cholecystitis; chronic arthritis; chronic enterocolitis	Pathological gall bladder.
10	25.0	None	Cholelithiasis; cystitis cancer bowel	Pathological gall bladder and stone; cancer bowel.
19	8.0	Pathological gall bladder	Pathological gall bladder; hemorrhagic pleurisy	Adhesions around gall bladder interfering with drainage.
49	10.0	Duodenal ulcer; pathological gall bladder	Duodenal ulcer; pathological gall bladder; chronic enterocolitis	Duodenal ulcer; pathological gallbladder.
28	26.6	Pathological gall bladder	Pathological gall bladder; chronic appendix	Pathological gall bladder only.
53	50.0	Cancer head pancreas; Cancer bile duct	Died. Autopsy proved findings pathological gall-bladder.
80	15.0 *7.6	Pathological gall bladder	Duodenal ulcer and adhesions	Duodenal ulcers; adhesions; inflamed gall bladder.

* No. 80 dropped to 7.6 on the fifth day after operation.

TABLE III.—NEGATIVE FOR GALL BLADDER.

No.	Icterus index.	Röntgen-ray.	Diagnosis.	Operative findings.
31	5.4	Pathological gall bladder	Toxic thyroid; chronic enterocolitis; fibroid tumor	Gall bladder normal; uterine fibroids.
47	7.4	Pathological gall bladder; duodenal ulcer	Duodenal ulcer; chronic colitis, colon stasis, chronic appendix	Chronic appendicitis; adhesions.
52	3.4	Gastric ulcer; pathological gall bladder	Chronic enterocolitis; gastric ulcer adhesions	Gastric ulcer; adhesions around gall bladder; gall bladder normal.
57	5.6	Gastric ulcer, colon stasis and adhesions; pathological gall bladder	Chronic arthritis; acute bronchitis; chronic enterocolitis	Gall bladder normal; pyloric stenosis; adhesions.
81	5.0	Chronic appendix; chronic enterocolitis	Gall bladder normal; chronic appendix.
66	6.0	Duodenal ulcer	Ruptured appendix	Appendicitis, otherwise O.K.
67	7.8	Gall bladder normal	Chronic appendix; double hydrosalpinx	Chronic appendicitis salpingitis.
68	6.4	Chronic appendix; colon stasis and adhesions	Chronic appendix; colon adhesions	Chronic appendicitis; adhesions.
11	5.4	Gall bladder and appendix	Gall bladder and appendix	Gall stones and appendix; gall bladder negative.
12	6.0	Gall bladder and duodenal ulcer	Appendix	Subacute appendicitis.
63	8.2	Colon stasis with adhesions	Chronic arthritis; chronic appendix; colon stasis	Chronic appendix; gall bladder normal.
65	7.0	Colon stasis with adhesions	Chronic appendix; chronic enterocolitis	Chronic appendix; ovarian cysts; gall bladder normal.
78	5.4	Chronic appendix	Gall stones, gall bladder normal in color. Bile normal in color. No infection.
79	6.2	Gall bladder normal; chronic appendix	Chronic appendix	Chronic appendix; gall bladder normal.

In our greater table that follows we desire to call attention to the fact that the blood nitrogen in these cases was not an instructive factor. There is only 1 luetic case (No. 71) in the entire group. Icterus began to appear clinically in nearly all cases when the index rose above 15. However, in some there was no visible jaundice when the index was much higher.

TABLE IV.

No.	Icterus index.	Diff. count.		Trans. per cent.	White.	Red.	Hb. per cent.	Stool.	Roentgen-ray diagnosis, probable.	Diagnosis.
		Polys. per cent.	Lymph. per cent.							
1	(7-17)* 13.0	65	27	7	9,800	4,270,000	80	Ameba histolytica	Pathological gall bladder	Chronic cholecystitis; chronic enterocolitis; acute bronchitis.
2	(7-26) 19.0	74	26	..	10,000	4,600,000	88	Negative	Duodenal ulcer; pathological gall bladder	Duodenal ulcer; chronic cholecystitis; chronic cholelithiasis.
3	(-9)15* (7-13)6.2† 13.5	50	43	4	5,600	4,290,000	82	Ameba histolytica	Pathological gall bladder	Chronic cholecystitis; chronic enterocolitis.
4	18.0	65	32	3	8,500	4,250,000	85	Negative	Pathological gall bladder	Chronic cholecystitis.
5	37.5	65	29	6	7,000	3,610,000	70	Negative	Pathological gall bladder	Acute cholecystitis.
6	15.0	66	32	2	6,200	4,160,000	80	Negative	Pathological gall bladder	Chronic cholecystitis; chronic arthritis; chronic enterocolitis.
11	12.0	84	16	..	13,600	4,160,000	80	Ameba histolytica	Chronic cholecystitis; chronic enterocolitis.
12	10.0	69	29	2	8,800	2,210,000	30	Trichomonas	Pathological gall bladder	Chronic cholecystitis; chronic enterocolitis, chronic myocarditis.
13	20.0 28.3	78	16	6	8,200	3,460,000	70	Tenia {saginata	Tenia saginata; chronic enterocolitis; chronic cholecystitis.
14	15.0† 20.0	58	42	..	7,000	3,210,000	68	Giardia, chilomastix	Pathological gall bladder	Chronic cholecystitis; chronic enterocolitis.
15	8.8	73	27	..	9,700	4,048,000	70	Ameba	Gall stones	Chronic cholelithiasis, chronic enterocolitis.
16	7.5	62	35	3	8,000	4,180,000	80	Negative	Duodenal ulcer; pathological gall bladder	Chronic cholecystitis; duodenal ulcer.
17	45.0	58	37	5	7,500	3,912,000	80	Ameba	Pathological gall bladder	Catarhal jaundice; chronic enterocolitis.
18	18.0	65	29	6	7,500	4,650,000	78	Chilomastix	Gall bladder	Chronic cholecystitis; enterocolitis.
20	100.0	75	25	..	12,000	3,210,000	60	Negative	Acute catarhal jaundice.
21	20.0	70	30	..	8,600	3,920,000	70	Negative	Chronic cholecystitis; rheumatic fever.
22	10.0	66	29	5	8,800	4,410,000	85	Negative	Pathological gall bladder otherwise negative	Chronic cholecystitis; chronic arthritis.

TABLE IV.—(Continued.)

No.	Icterus index.	Diff. count.		Trans. per cent.	White.	Rcd.	Hb. per cent.	Stool.	Roentgen-ray diagnosis, probable.	Diagnosis.
		Polys. per cent.	Lymph. per cent.							
23	20.0	70	25	5	7,000	3,160,000	55	Negative	Positive for gall bladder; shadow	Chronic cholecystitis; chronic enterocolitis.
24	22.0	71	27	2	7,000	3,880,000	68	Ameba histolytica	Positive for gall bladder; shadow	Chronic cholecystitis; chronic enterocolitis.
25	24.0	68	32	..	7,800	4,250,000	75	Ameba	Negative for gall bladder; colon stasis	Chronic cholecystitis; chronic enterocolitis.
26	18.0	61	37	2	8,200	4,280,000	82	Negative	Chronic cholecystitis; chronic enterocolitis.
27	14.0	66	30	4	7,800	4,580,000	90	Craig	Chronic cholecystitis; chronic enterocolitis.
29	19.0	72	26	2	12,000	5,020,000	90	Negative	Chronic cholecystitis; chronic enterocolitis.
30	15.0	79	18	3	5,400	3,580,000	70	Ameba histolytica	Duodenal ulcer; pathological gall bladder	Chronic cholecystitis; chronic enterocolitis; duodenal ulcer.
32	6.6	60	35	5	9,000	4,410,000	83	Ameba histolytica; trich. chilomastix	Chronic enterocolitis.
33	6.6	56	38	6	7,600	4,210,000	85	Chilomastix	Chronic enterocolitis.
34	5.4	72	25	3	9,400	4,948,000	80	Ameba	Chronic enterocolitis.
35	6.0	87	13	..	16,000	4,470,000	77	Ameba	Chronic enterocolitis; acute bronchitis.
36	5.7	61	36	3	7,800	4,120,000	80	Ameba	Chronic enterocolitis.
37	4.2	62	35	3	6,900	3,544,000	70	Ameba	Chronic enterocolitis; epilepsy.
38	7.5*	70	29	1	10,400	4,320,000	85	Negative	Pathological gall bladder; colon stasis	Chronic enterocolitis; hernia from appendectomy.
39	5.1†	14,800	3,920,000	..	Ameba	Acute bronchitis; chronic enterocolitis.
40	6.6	16,800	4,290,000	90	Trichomonas	Chronic enterocolitis; acute pleurisy.
41	5.0	58	42	..	7,500	4,250,000	75	Negative	Negative for gall bladder	Chronic enterocolitis.
42	8.0	64	35	1	5,600	4,620,000	92	Ameba	Negative for gall bladder	Chronic enterocolitis.
43	6.0	62	34	4	8,256	4,250,000	80	Ameba	Chronic enterocolitis.
44	7.0	50	47	3	7,100	4,520,000	75	Negative	Duodenal ulcer; colon stasis; no gall bladder	Duodenal ulcer; colon stasis.
45	8.4	59	27	2	6,200	3,990,000	75	Ameba	Duodenal ulcer; chronic enterocolitis	Duodenal ulcer; chronic enterocolitis.

46	9.4	64	31	2	6,600	4,680,000	70	Negative	Duodenal ulcer; no gall bladder	Duodenal ulcer.
48	7.0	72	28	..	7,100	4,864,000	80	Ameba	Myocarditis	Chronic myocarditis, duodenal ulcer, chronic enterocolitis.
50	4.2	73	26	1	9,200	5,904,000	65	Ameba	Gastric ulcer; no gall bladder; colon stasis	Gastric ulcer; colon stasis; chronic enterocolitis; acute bronchitis.
51	4.4	82	15	3	13,600	3,190,000	56	Chilomastix	Gastric ulcer; no gall bladder	Gastric ulcer, varicose ulcer chronic enterocolitis; chronic nephritis.
54	19.8* 18.5†	63	37	..	6,600	5,088,000	65	Negative	Myocarditis, mass in hepatic region possible; cancer; fluid right chest	Cardiac failure, hydrothorax; general anasarca, malignant of liver.
55	10.0	10,200	5,920,000	..	Trichomonas	Myocarditis	Cardiac failure; chronic enterocolitis, hypertension.
58	4.0	74	25	..	6,300	4,432,000	75	Chilomastix	Negative except joints	Chronic arthritis; chronic enterocolitis.
59	3.4	67	33	..	9,900	5,848,000	85	Chilomastix	Negative except joints	Chronic arthritis; chronic enterocolitis.
60	7.5	60	38	2	5,500	4,144,000	80	Ameba histolytica	Chronic arthritis; chronic enterocolitis.
61	6.2	62	38	..	4,500	4,520,000	75	Ameba histolytica	Chronic arthritis; chronic enterocolitis.
62	6.6	60	38	2	7,600	4,064,000	85	Giardia cysts	Chronic appendix, negative gall bladder; colitis	Chronic arthritis; chronic appendix; chronic enterocolitis.
64	5.0	66	34	..	5,400	4,736,000	85	Chilomastix	Chronic arthritis; chronic enterocolitis.
69	4.8	Carcinoma bowel	Metastatic carcinoma bowel, secondary anemia.
70	5.4	88	12	..	12,400	2,632,000	..	Negative	Broad ligament abscess general peritonitis, secondary anemia.
71	4.2	66	34	..	9,100	3,880,000	75	Negative	Syphilis, pyelitis.
72	8.2	59	41	..	8,300	4,262,000	80	Ameba	Kidney stone	Chronic enterocolitis; kidney stone, renal colic.
74	19.0	58	42	..	4,400	1,904,000	..	Ameba	Negative for gall bladder and kidney stone	Pernicious anemia, chronic enterocolitis.
75	9.4	66	34	..	4,900	1,472,000	..	Trich. chilomastix	Arthritis, malignant liver	Pernicious anemia, chronic enterocolitis, chronic arthritis.
76	9.0	67	33	..	3,600	2,022,000	60	Negative	Apical abscess, colitis, mass in liver	Pernicious anemia, apical abscess, chronic enterocolitis.
77	5.6	84	14	2	16,400	3,200,000	70	Negative	Diabetic gangrene, chronic interstitial nephritis.

No. 71, Wassermann positive 4+.

* Index taken during attack.

† Index taken after attack.

Conclusion. We feel that this test is a valuable aid in differential diagnosis where there is pathology influencing the function of the liver. It is certainly highest in biliary diseases. The index returns to normal after such pathology has been removed. Gall stones that show no evidence of obstruction or active inflammation do not influence the index. Adhesions about the duodenum or gall bladder may by the blocking of ducts cause a rise in the index. Here the index may be an aid in differentiation between gastric and duodenal ulcer.

The uncomplicated secondary anemia show a hypobilirubinemia. This test helps to explain the presence of the Diazo reaction in the urine of typhoid patients, and by this fact it becomes much more diagnostic in this disease. With the Widal hemoclastic test it becomes measurably prognostic and aids in treatment.

The leukopenia of typhoid, malaria, etc., may be a direct physiological influence of the hyperbilirubinemia.

In closing we desire to express our grateful appreciation to our technician, Miss Estella Campbell, and to our pathologists, Drs. Brem, Zeiler and Hammock, for their scientific and painstaking care in the laboratory preparation of this work.

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REVIEWS.

ANGINA PECTORIS. By SIR JAMES MACKENZIE, M.D., F.R.S., F.R.C.P., LL.D., F.R.C.P.I., Director, St. Andrew's Institute for Clinical Research, Consulting Physician to the London Hospital and to H. M. the King in Scotland. Pp. 253; 77 illustrations. London: Henry Frowde, Hodder & Stoughton, Oxford Medical Publications, 1923.

MACKENZIE's death before it was possible to write for this journal a review of his latest book, which only reached us in January, demonstrates how actively he was employed to the very end. Though this is not the place to expatiate on the virtues of this eminent cardiologist, the reviewer cannot refrain from lamenting this great loss to medical science, at the same time expressing appreciation of the forethought which founded the St. Andrew's Institute for Clinical Research, and thus ensured that his good works would continue after him.

Books from Mackenzie's pen have always been interesting and useful because one could be confident that the statements were the author's own and not borrowed from others and that they had the valuable background of long experience as well as a very original mind. The present volume is no exception to the rule and constitutes a valuable addition to the study of angina pectoris. Nevertheless, the very defects of the author's virtues make it necessary for the reader to beware of accepting as settled many of the dogmatic statements about subjects which are still open questions; and for him to remember that much valuable evidence from other sources is not only not mentioned but apparently had not even been known to the author.

Assuming thirty years ago from the divergence of opinion on the subject of angina that the method of inquiry was defective, Mackenzie started from the new point of view of investigating pain, as the most prominent feature of the condition. This naturally led him to inquire what were the structures concerned, what kind of stimulus was adequate to produce the pain, how it was conveyed to the sensorium, what conditions led to its production and what effect it had on the patient's life. This in turn led him back to the underlying question of heart failure, where he was so impressed with the "woefully defective" state of our knowledge that he laments "that no real advance can be made in our knowledge of

angina pectoris, or, indeed, in any matters concerned with the heart" clinically, until the matter is remedied. (This from one who has added so much to our knowledge of the mechanism of the heart beat and heart failure is significant and characteristic.)

Nevertheless in the present book he developed these ideas, which led him to formulate his now well-known view that the pain of true angina is due to heart muscle contraction in the absence of sufficient blood supply—usually occurring, to be sure, as a result of coronary disease, but possibly also from a direct exhaustion or degeneration of the heart muscle with normal coronaries. The heart pain noticeable to a hypersensitive nervous system, he labels secondary angina pectoris (in other words, the older "pseudo-angina") and here does not consider the heart primarily at fault. In order to explain the production of the pain, the theory of disturbed reflexes—enthusiastically pursued but not really invented at the St. Andrew's Institute—is invoked, the exhausted muscle supplies the stimulus, which is felt as pain in the appropriate referred zone, the stronger the stimulus the larger being the zone affected.

On this basis an interesting, stimulating and instructive structure is reared, which will be of permanent value to students of the subject. The appendix of almost 100 pages with records of 160 cases is one of the most valuable features. The easy style, fundamental method of treatment and pleasant make-up of the book add to its readability.

E. K.

THE THEORY OF DECREMENTLESS CONDUCTION IN NARCOTIZED REGION OF NERVE. By GENICHI KATO, Professor of Physiology, Director of Physiological Institute, Keio University, Tokyo, Japan. Pp. 166; 126 figures and tables. Nankodo, Hongo, Tokyo, Japan, 1924.

PROFESSOR KATO's experiments disprove the hitherto accepted notion that in traversing a partially and uniformly narcotized region the nerve impulse undergoes progressive decrease in intensity. Instead, the impulse, though subnormal, is constant throughout the region. Through a series of careful tests, the sources of error in the previous evidence are made clear. One of these tests incidentally offers a new line of evidence for the all-or-none law in nerve, in place of Adrian's previous apparent proofs, now rendered invalid by Kato's disproof of decremental conduction. Moreover, the all-or-none law is shown to hold also in narcotized nerve—thus our notions of nerve conduction are helpfully unified. The implications of this work as to the properties of the synapse are not as revolutionary as might be supposed—for example, the facts of Wedensky inhibition, not treated by Kato, remain, though they need some reinterpretation.

Some minor shortcomings of method and proof are to be condoned in view of the magnitude and clear-cut result of the work as a whole, which should prove a great stimulus to the advance of nerve physiology.

D. B.

A TEXTBOOK OF VERTEBRATE EMBRYOLOGY TREATED FROM THE COMPARATIVE STANDPOINT. By RUTH L. PHILLIPS, Ph.D., Professor of Biology, The Western College for Women, Oxford, Ohio. Pp. 302; 137 illustrations. Price \$3.50. Philadelphia, and New York: Lea & Febiger, 1925.

THIS compact little book, clearly and accurately written and well got up by the publisher, should be of value to biologists needing embryological information, as well as to the students for whom it was designed. Though "written with the idea of furnishing a short, concise test to supplement the all-important work of the laboratory," it should frequently be useful in obviating longer search in the more exhaustive textbooks of the subject, many of which are rather hopelessly out of date. Following a short historical sketch, are four chapters on cell development through the embryonal membrane stage, with a second part of seven chapters on organogeny.

E. K.

MATERIA MEDICA FOR NURSES. By A. L. MUIRHEAD, M.D., Late Professor of Pharmacology, Creighton Medical College, Omaha, Nebraska and EDITH P. BRODIE, A.B., R.N., Washington University School of Nursing, St. Louis, Missouri. Second edition. Pp. 190; 25 illustrations. St. Louis: The C. B. Mosby Company, 1924. Price \$2.00.

THE purpose in revising this book seems to have been to reclassify the drugs according to their action on the various systems, to include in the discussion a brief review of the physiology of the system and to add new sections on the preparation of solutions and dosage. About one-fourth of the entire book is devoted to material usually covered in the course in drugs and solutions. The text is concise, readable and accurate. The chief criticism is the brevity and elementary character of the material. However, the authors state it has been their aim to provide the student with an adequate working knowledge of the subject "in the simplest and briefest form and at the same time to meet as satisfactorily as possible the recommendations for instruction in Materia Medica outlined in Standard Curriculum for Schools of Nursing." This book would need to be supplemented by additional material to fulfill the latter function.

S. G.

SURGICAL PATHOLOGY. By WILLIAM BOYD, M.D., M.R.C.P. (ED.), F.R.S.C., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Pp. 837; 349 illustrations and 13 colored plates. Philadelphia and London: W. B. Saunders Company, 1925. Cloth, \$10.00 net.

THE appearance of two new large books on Surgical Pathology within a twelve-month inevitably invites a comparison between them. While books of the caliber of McFarland's and Boyd's would in any case be welcome additions to a subject which has hitherto been but poorly represented in the medical literature of the English speaking world, they are especially so in that they approach the subject from somewhat different points of view (both mental and geographical) and to that degree are complementary. As compared with McFarland's work (see review in AM. JOUR. MED. SCI., 1924, 168, 603), Boyd has dealt with the subject matter in a more systematic and inclusive manner, thus offering a greater chance that the query of the person seeking information will be answered, even though that answer may be less original and forceful. Even the illustrations are cases in point, being not infrequently borrowed from other sources, but of such appropriateness and excellence that they correspondingly improve the ensemble of the book.

The first quarter of the book is devoted to twelve chapters on General Pathology, on such subjects as bacteriology, inflammation, healing, tuberculosis, syphilis, shock, tumors. In the remaining three-quarters—twenty-five chapters on Special Pathology—special systems, individual organs and single diseases are discussed. A chapter on nerve pathology is conspicuous by its absence, though a few nerve tumors are treated in the first section.

In a short foreword, Dr. W. J. Mayo points out that Dr. Boyd has tried to produce "a work that will serve as a handbook to the surgeon, and the internist, and a guide to the beginner in the (this?) field of medicine." For this reason perhaps the very elementary treatment of the chapter on bacteriology may be justified; otherwise it would seem that the cursory descriptions of the common organisms mentioned might better have been either amplified or omitted. There is even less justification for calling the pneumococcus a small oval coccus, or to speak on one page of the "failure of the Gram-positive and acid-fast bacteria to stimulate the body to an immunity response" and on the next to assert that "it is in staphylococcal infections of the skin that some of the most gratifying results of vaccine therapy have been obtained."

The book is admittedly "didactic in tone, as is necessary in a volume of this scope, not judicial, fortunately, because to be judicial one must deal only with proved facts and give no play to scientific imagination." Leaving aside the objection naturally to be made to the latter statement, one can emphasize that here, as in most

medical works, didactic treatment calls for a corresponding reserve of acceptance on the part of the intelligent reader. Exception might be taken also to the implied slight in the Foreword to the value of the postmortem room and the "cadaverization" of biopsy specimens, if by this phrase is meant the examination of biopsy specimens in paraffine as well as in frozen sections. Broader and more logical is the opinion of the author who, fully unholding the value of Moynihan's "pathology of the living" and the advances that it has caused, nevertheless still recognizes that "the fundamentals of pathology must be learned in the postmortem room," where the disease process, end-results though it may be, "can be seen as a whole, and the clinical picture viewed in a way that will often make light the dark places of the case."

To the actual treatment of his subjects, the author has brought an easy style and a philosophical, historical flavor that pleasantly illuminate the results of his extensive study of the works of others, and his considerable personal experience. The influence of the best modern leaders in pathology and of the medical experiences of the war can be read in and between many lines.

"References for further study" at the end of each chapter are purposely made brief "to induce the reader to go further afield in his search for knowledge." To the reviewer, it would seem more appropriate to lengthen these lists, even at the risk of "seeming to display the erudition of the writer," in order to aid the reader in going much further afield. Inducement should not be necessary to those most worth catering to.

As is usual with Saunders books, the make-up leaves little to be desired; the paper is good, the type pleasing and well placed, the index adequate, the illustrations attractive and true to life and yet demonstrate what they are supposed to demonstrate. All in all the book well fulfills its object "to present those aspects of pathology which will prove useful to the surgeon" and should be of value to the pathologist as well.

E. K.

HUMAN CONSTITUTION. By GEORGE DRAPER, M.D., Associate in Medicine at Columbia University, New York City. Pp. 345; 208 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

THIS book is written for the purpose of outlining a uniform scheme whereby physicians interested in the human body might have a model upon which to base their observations. No attempt, says the author in his preface, is to be made to develop a method of diagnosis, "although obviously in the train of a study of constitution aids to diagnosis will appear." Following out this declared intention, the book is divided into seven chapters; the first few deal with

the general principles of anthropological measurements, order of examination, methods of examination and analyses of the curves. A very long chapter now follows discussing many charts and containing the kernel of Dr. Draper's researches. In this chapter, the variations that occur in the measurement of different individuals suffering from six diseases—gall bladder, peptic ulcer, nephritis, pernicious anemia, tuberculosis and asthma—are verbally discussed and graphically illustrated. They are interesting and instructive and yet one would be rather inclined to look with a certain skepticism upon deductions that are drawn from such a few cases; for example, gall bladder disease, 17 cases; pernicious anemia, 21 cases and so on, in spite of the prefatory defense of the method "of combining accumulative percentage curves and relative frequency curves . . . by means of which, with a smaller number of observations than have heretofore been acceptable, significant differences can be readily interpreted." A further criticism might be added: The art of measurement is a difficult one and probably few clinicians would be willing to devote the time and the care, nor would they have the ability to make such exact and minute measurements as are apparently required.

An objection or two to this work has been cited. Yet Draper has done a real service to medicine in attempting to put upon a scientific basis the study of anthropometry. It was not so many years ago that the clinician was speaking familiarly but in the most general terms of the lymphatic habitus, the apoplectic, the enteroptotic or the phthisical; but it has remained for the author of this little book to study scientifically the so-called habitus of the patient. In 1761 Auenbrugger wrote upon immediate percussion, a great discovery which remained unnoticed until Corvisart, in 1808, brought it again before the eyes of the medical world. Perhaps Draper will be the Corvisart who will show generations to come that anthropometry is an invaluable aid to diagnosis.

J. M.

A MANUAL OF PSYCHIATRY. By PAUL E. BOWERS, M.S., M.D.,
Lecturer in Neuropsychiatry, Post-Graduate Medical School of
the University of California. Pp. 365. Philadelphia and London:
W. B. Saunders Company.

BRIEFLY and clearly, the accepted views regarding mental diseases are here set forth, controversial material being eliminated. The compact form, and systematic method of treatment will commend this work to the student or practitioner who desires a readable and reliable handbook of Psychiatry.

J. A.

OPERATIVE SURGERY. Covering the Operative Technic Involved in the Operations of General and Special Surgery. By WARREN STONE BICKHAM, M.D., F.A.C.S., Former Surgeon in Charge of General Surgery, Manhattan State Hospital, New York; Former Visiting Surgeon to Charity and to Touro Hospitals, New Orleans. In 6 octavo volumes totalling approximately 5400 pages with 6378 illustrations, mostly original and separate Desk Index Volume. Volume VI, completing the set, contains, 989 pages with 1224 illustrations. Price \$60.00. Philadelphia and London: W. B. Saunders, Company, 1924.

BICKHAM's Operative Surgery is now complete with the appearance of the sixth volume and index. This volume maintains the standard set by its predecessors. It deals chiefly with Neurological, Gynecological and Orthopedic Surgery. The latter is only a sketchy summary. It could hardly be used as a satisfactory guide for work in this field. The remainder of the book is the usual compilation of recognized operations well described and pictured. Considerable maturity of surgical judgment is required in the employment of a work of this kind owing to the necessity for selection of the operation to fit the case. This is, however, not a criticism. As a thesaurus of operative methods it is invaluable. The index is well done and adds greatly to the utility.

D. P.

MONOGRAPHS ON SYSTEMATIC BACTERIOLOGY, VOLUME I, GENERAL SYSTEMATIC BACTERIOLOGY. By R. E. BUCHANAN, PH.D., Professor of Bacteriology, Bacteriologist of the Iowa Agricultural Experiment Station and Dean of the Graduate College, Iowa State College, Ames, Iowa. Pp. 597. Baltimore: Williams & Wilkins Company, 1925.

THIS volume represents the first of a series of monographs prepared under the sponsorship of the Society of American Bacteriologists dealing with the general field of systematic bacteriology. The first chapter deals with the history of the various classifications of bacteria which have been proposed up to the present time, bringing together much material from widely scattered sources which have been for the most part difficult of access. In the second chapter codes of nomenclature are presented, while the third and final chapter presents an alphabetical list of the names used by various authors to designate bacterial subgenera, genera, and higher groups compiled from a comprehensive study of the literature. An extensive bibliography is appended.

J. S.

THE PRACTICE OF PEDIATRICS. By CHARLES GILMORE KERLEY, M.D., Attending Physician, to the New York Nursery and Child's Hospital, and GAYLORD WILLIS GRAVES, M.D., Associate in Diseases of Children in the College of Physicians and Surgeons (Columbia University). Third edition. Pp. 922; 150 illustrations. Philadelphia and London: W. B. Saunders Company.

THE third edition of this standard work on pediatrics contains much that is new, and much of the text of the previous edition has been rewritten. The recent advances in our knowledge concerning scarlet fever, diphtheria, diabetes, rickets and many other diseases will be found included in these pages, while many of the older articles and illustrations have been omitted. As a clear and authoritative textbook on pediatrics this edition will appeal even more than its predecessors to the general practitioner, pediatrician, and medical student.

J. A.

PRACTICAL SURGERY ILLUSTRATED. By VICTOR PAUCHET. Translated by F. R. B. ATKINSON, Volumes I and II, pp. 545; 416 illustrations. London: Ernest Benn Limited, 1924.

THIS unique work carries with it unusual interest in view of the fact that it is the product and the representation of one man's activities. He describes and illustrates in a most profuse fashion actual operations performed by the author and other French surgeons. All of the illustrations are absolutely new; in fact, have been created at the time of that particular operation. They are large, some of them being full-page size which is an advantage in that a greater amount of minutiae and detail can be portrayed. The text itself takes a minor place when the value of this work is considered. In fact, the text constitutes but a very small proportion of the page space in these volumes. Its one idea is to describe the illustrations. The books as volumes are distinct and each one sufficient unto itself. It can in no way be considered a system of surgery but, however, fills a most important place in the surgical armamentarium of today. It is a good, comprehensive and clearly presented operative surgery.

E. E.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Skin Infection of Rabbits with Hemolytic Streptococci Isolated from a Patient with Erysipelas.—T. M. RIVERS (*Jour. Exper. Med.*, 1925, 41, 179) describes a method of demonstrating protective action of immune sera with an organism which he isolated from a human case of erysipelas and which culturally and morphologically resembles hemolytic streptococci. He first shows that cultures of this organism when injected intracutaneously into the shaved abdomen of the rabbit, produced nine times out of ten large severe abscesses. In the tenth case a lesion would be produced which was characterized by redness and swelling of the skin outside the phlegmonous area, extending in all directions, the advancing margin being irregular and slightly red. The lesion would continue to spread for six to seven days and then subside. This was followed by a marked desquamation of the involved skin. This lesion, as described above, appears to be truly characteristic of the lesion that is seen in cases of human erysipelas. The next step in this study was the production of an immune serum by injecting intracutaneously 0.2 cc of a suspension of the streptococci, making in all 7 injections, seven days apart. Eight days after the last injection the animals were bled and their sera pooled. The immune serum was then mixed with varying dilutions of the streptococci and injected intradermally. For controls, equivalent mixtures of normal sera and streptococci were employed. The control areas were all characterized by the formation of large nodules filled with pus and covered with scabs. The areas inoculated with the immune serum mixture showed little change from the normal skin. Should this method of demonstrating the

immune properties of antistreptococcic serum prove of general applicability, Rivers writes that it will possess a number of advantages which are absent from the ordinary methods of testing for protective action of sera. It may be not only a method of testing the potency of sera for therapeutic purposes, but also a method of testing the specificity of different strains of the streptococcus.

Local Passive Immunity in the Skin of Rabbits to Infection with (1) a Filterable Virus, and (2) Hemolytic Streptococci.—In another communication on somewhat the same general lines as the one abstracted above, RIVERS (*Jour. Exper. Med.*, 1925, 41, 185) shows that when small areas of skin are infiltrated with normal serum of meat broth these areas are more refractory than normal skin to infection with hemolytic streptococci, a nonspecific reaction which is, however greatly intensified if a homologous immune serum is employed. The author very pertinently suggests that in erysipelas it might be possible to prevent the spread of the infection by injecting at the margins of the healthy skin immune serum which would make it refractory and prevent further spread of the infection.

Contributions to the Pathology of Experimental Virus Encephalitis. I. An Exotic Strain of Encephalitogenic Virus.—S. FLEXNER and H. L. AMOSS (*Jour. Exper. Med.*, 1925, 41, 215) during the course of an extensive research upon the etiology of epidemic encephalitis, in which 100 specimens of cerebrospinal fluid were injected into rabbits, obtained an exotic virus from the fluid of an individual suffering from cerebrospinal lues who at no time had symptoms other than those referable to his syphilitic infection. This was the only virus which was capable of producing an inoculable disease and it was found in only one of three different specimens of the cerebrospinal fluid obtained from the same source. The finding of this exotic virus, the J. B. virus, apparently serves "to clarify the obscurity and confusion now enveloping the so-called virus of encephalitis." This virus, as is shown by the authors, differs biologically in no way from the virus of herpes and encephalitis. It is apparently a herpes virus which has entered the cerebrospinal fluid and, if such is the case, it shows that the virus obtained by others is probably merely another instance of the ubiquitous herpes virus entering the spinal fluid and discovered by chance. The J. B. virus possesses a strong affinity for the brain structures of the rabbit, but as it was isolated from a patient presenting none of the symptoms of epidemic encephalitis, it seems highly probable that the herpetic virus has a different action on the brains of the two species, man and rabbit. There is no warrant for ascribing epidemic encephalitis in man to a virus which is apparently merely a type of herpetic virus solely because it produces marked cranial disorders in rabbits. To the experimental disease produced in rabbits by the inoculation of the herpes and allied viruses, Flexner and Amoss propose the name Virus encephalitis.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Intravenous Continuous-drop Infusion.—EICK (*Centralbl. f. Chir.*, 1924, 47, 2575) describes simple apparatus and refined technic for this procedure. The author uses routinely a trade preparation called Calorose, a mixture of equal parts of dextrose and levulose. Figures are cited of 18 cases saved by this procedure in a series of 82 moribund patients. The author, however, feels that the procedure as a routine after operations has distinct merit, especially in long continued operations with loss of much blood. In cases of ileus, peritonitis or uremia, good results have been reported. The procedure is contraindicated in heart, lung, and kidney disorders.

Roentgenologic Diagnosis of Cholecystic Disease with the Aid of the Sodium Salt of Tetrabromophenolphthalein.—CARMAN and COUNSELLOR (*Am. Jour. Roentgenol.*, 1924, 12, 403) state that the dye should not be used in cases where obstruction was known to exist. The typical severe reaction is one of vasomotor shock. It usually begins within five to ten minutes. Normally the gall-bladder will retain sufficient dye to cast a shadow at the fourth or fifth hour after administration. This shadow attains its greatest intensity sometime between the eighth and twenty-fourth hours. It becomes thinner thereafter and should disappear between the twenty-fourth and forty-eighth hours. The shadow is oval or pyriform with an even contour and should be homogeneous. It is larger at earlier than at succeeding hours. This variation in size is important evidence of normal distensibility and contractability. Abnormal responses include failure of the gall bladder to fill with the dye, scanty filling as shown by persistent faintness of the shadow, delayed filling, marked delay of emptying, deformity of contour, unvarying size of shadow, constant extremes of size and mottling or central defects. In the absence of cirrhosis or gross impairment of hepatic function, interference with filling suggests obstruction due to gall stones, adhesions, new growths, thickened bile or other pathological conditions. Unvarying size of the shadow implies loss of elasticity of the gall bladder walls. Mottling of the shadow suggests stones or papillomas.

Splenectomy in Egyptian Splenomegaly.—COLEMAN and BATEMAN (*Lancet*. 1924, 1116) state that splenectomy has been advised in all suitable cases since 1920. Probably 50 per cent of those seen in outpatient departments are refused operation at once, owing to definite

contraindications, considerable ascites, pellagra, disease of the heart, and advanced general debility. The remainder are advised admission for observation and further examination and the majority agree to this. Most are suffering from ankylostomiasis and bilharziasis, either rectal or urinary and these diseases are treated before the blood is examined. Preliminary treatment takes two or three weeks, as a rule. The authors have learned from experience to know beforehand from the shape of the spleen, which are difficult cases. A spleen very long from above downward means a long pedicle, and can be tackled piece by piece. But a broad spleen extending medially beyond the midline means a thick, bunched-up pedicle in which the vessels are difficult to reach and secure individually. The spleens removed have varied from $1\frac{1}{4}$ pounds to $12\frac{1}{2}$ pounds. The average for the series is $3\frac{3}{4}$ pounds. The mortality is still high, but untreated cases so easily develop extreme ascites that the operation is justifiable.

The Sacro-iliac Joint: Its Diagnosis as Determined by the Roentgen-ray.—DARLING (*Radiology*, 1924, 3, 486) says that backache has more to do with the soft tissues, ligaments, muscle fibers, bundles and sheaths, nerves and neuralgia than dislocations of joints. Sprains, sacro-iliac and lumbosacral, seem more likely than demonstrable relaxations or subluxations. The sacro-iliac joint has a synovial lining and is, therefore, subject to arthritis, due to any focus of infection. Sacro-iliac strain, relaxation, subluxation or dislocation may exist clinically, but cannot be shown definitely by the roentgen-ray examination if and where the motion consists of a forward and backward tilting of the sacrum, in relation to the ilium. Where there is actual separation of the pelvic girdle, such as complete fracture with displacement or a complete separation at the symphysis, then only will there be shown by roentgen-ray a definite sacro-iliac separation relaxation. Radiographs made improperly are often misinterpreted as showing separations, which do not exist. This is a too common error, due to zealous attempts to make or support a diagnosis.

Necrosis of the Kidney.—FALCI (*Jour. d'Urol.*, 1924, 18, 449) declare that total destruction of the kidney from renal infarct follows a definite infection of the cardiovascular type as a general rule. Cases following specific diseases, such as diphtheria or scarlet fever, are extremely rare. The symptoms and signs are not definite to a pathognomic degree. Onset is rapid, course violent, while pain has its location in the renal area. The urinary findings are significant. Diagnosis, while difficult, is essentially possible, especially if the previous medical history and cardiovascular findings are weighed judiciously. The prognosis is exceedingly grave, 86 deaths in 100 collected cases. Nephrectomy is the treatment in unilateral necrosis of the kidney.

Ideal Prostatectomy.—BURK (*Centralbl. f. Chir.*, 1925, 52, 113) states that the primary closure of the prostate bed and the wound in the bladder makes a great advance in the field of prostatic surgery. Merten of Bremen has brought forward this method with report of follow-up studies, upon his cases. The advantages of the method lie in prevention of infection in the space of Retzius and in the layers of abdominal

wall, factors which have destroyed the lives of aged, weakened patients. Other favorable features of this procedure are the reduction in time of illness and the severity of the illness. Secondary hemorrhage from the prostatic bed is the cardinal danger in this method, as described by Merten. The present author does not feel that the simple suturing of the mucous membrane in the base of the bladder is sufficiently safe, for the bleeding is usually marked enough to prevent extremely accurate suturing. He then describes an evolved technic for bringing the prostatic bed well into view and under excellent control by rectal instrumentation. He reports the after course of several cases.

Operation upon Recent Patellar Fractures with Sutures of Fascia Lata.—VORSCHÜTZ (*Centralbl. f. Chir.*, 1925, 52, 179) says that treatment has become essentially operative. The series of operative cases collected by Thiem showed a mortality of 10 per cent, while unoperated series showed a mortality of 3 per cent. He discusses the merits of the encircling suture and the process of passing sutures through the fragments. He discusses the choice of suturing materials. He gives in detail the studies upon wiring and its after course. He shows that the fascia can give certain results that the wire cannot, for the fascia is not "foreign body" and therefore can be incorporated in the organic processes of the body. While the wire in the course of time, becomes attenuated and loosened by chemical processes and other forces, the fascia becomes firmer and tighter because it enters into the fibrous organization, holding the fragments more tightly as the process continues.

Abduction Treatment of Fracture of the Neck of the Femur.—WHITMAN (*Ann. Surg.*, 1925, 81, 374) states that the results even in the cases treated for fracture, as distinct from those in which the saving of life has been the first consideration, have always been extraordinarily bad. Neglect of the fracture passed as consideration for the patient, functional disability as an inevitable consequence of the injury and nonunion as evidence of incapacity for repair. The inception of a radical reform dates from 1890, when the author identified a fracture of the neck of the femur in a young child and reported it as a surgical curiosity. The incomplete or impacted fracture caused disability, not because of direct shortening, but because the deformity checked the range of abduction and induced an accommodative distortion of the limb. Nonunion in childhood could not be explained by insufficient nutrition, but was evidently the result of separation of the fragments. It was equally evident that conventional methods were inadequate either to correct the resistant deformity of the incomplete fracture, or to oppose displaced fragments securely. The author compares the series of Campbell with that of Smith, and early Victorian authority, whose mortality was 63 per cent. He makes this graphic contrast because the conventional practice has not materially changed in the interval and because it is still generally assumed that efficient treatment of the fracture is more dangerous than life-saving neglect. The abduction treatment is rarely described in practical detail in textbooks and either by inadvertence or intention, various modifications have been introduced, none of which appears to offer any advantage over the original but quite the contrary.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Energy Metabolism of Normal Newborn Babies, with Special Reference to the Influence of Food and of Crying.—MURLIN, CONKLIN and MARSH (*Am. Jour. Dis. Child.*, 1925, 29, 1) describe some improvements in the respiration apparatus designed to make measurements of oxygen absorption more accurate. The maximum error in the measurement of oxygen, and therefore on the heat production, is approximately 5 per cent. Two hundred and thirty-four observation periods on 50 newborn infants, ranging in age from six hours to fifteen days, are recorded. Of this number only ninety-eight periods with 38 infants may be described as truly basal, where the infant slept quietly throughout. The basal metabolism for these 38 infants averaged 6.67 calories per hour, or 2 calories per kilogram and 29.16 calories per square meter per hour. The respiratory quotient in these basal periods ranges from 0.66 to 1.16. The average of all quotients whether basal or not was from 0.79 the first twenty-four hours to 0.75 on the fourth day and then gradually upward to 0.85 on the ninth day. The basal heat production was highest in the second twenty-four hours. From this point it fell gradually and uniformly on the basis of surface to the sixth day, from which point it rose steadily. Applying statistical methods, it was found that, lumping all observations together, there was practically no correlation between heat production and the pulse rate. With regards to the influence of crying on energy metabolism, the interesting observation was made that in the average normal infant active healthy crying required just as much expenditure of energy as the basal metabolism while asleep. Expressed differently, crying 1 per cent of the time raised the metabolism 1 per cent. Special attention was given to the effects of natural food and of supplementary feeding of lactose and dextrose solutions on the respiratory quotient and on the basal heat production. It was found particularly difficult to raise the respiratory quotient by means of single supplementary feedings on the second and third days. The respiratory quotient accurately determined may be taken as an index of the state of nutrition. If sufficient food is given to insure a respiratory quotient of 0.9 or above within two and a half hours after feeding the state of nutrition will be good and the child will be gaining weight. The dynamic action of ordinary feedings or of supplementary feedings within the first eight days is very small. The largest recorded was 12 per cent from a feeding of 10 per cent lactose. The same was found with dextrose. Comparing the effects of small feedings, averaging 26.7 gm., of food or of the sugar solutions with that of larger feedings, averaging 51 gm., the increase in the basal heat production, due to the addition of 24 gm. was approximately 7 per cent average.

Studies in Tuberculosis: The Significance of Lymphangitis Occurring with Cutaneous Tuberculin Tests in Children.—EBERSON (*Am. Jour. Dis. Child.*, 1925, 29, 29) claims that the obvious deduction from his clinical and experimental study of tuberculin reactions and associated lymphangitis was that the phenomenon was specific and had some diagnostic as well as therapeutic significance. An interpretation of this observation presupposes a knowledge of facts which may have some bearing on the mechanism of a tubercle infection in relation to lymphatics and lymph glands. A search of the literature does not produce pertinent data regarding lymphangitis in relation to this phase of the problem. Conheim pointed out long ago that the tubercle bacillus leaves its mark on the lymph glands and the afferent trunks which drain the site of entry of the infection. Tubercle bacilli have been found to take a direct path to the proximal gland in their course along the lymphatics by means of phagocytic cells. In this process some organisms are destroyed, while those that are not give rise to a tuberculous focus in the lymph gland. The toxin which is produced by the bacilli causes lymphocytosis, which in turn serves to reduce the vulnerability of an adjacent gland as a result of a narrowing of the sinuses. It is not mere speculation to state that such a mechanism entails local as well as a more widespread sensitization, of which the phenomenon of lymphangitis appears to be an objective demonstration. It is of further interest in this connection to consider the question of what relation, if any, exists between the severity of a tuberculin reaction and the specific infection with tuberculosis. It would seem that there is some justification for stressing the value of correlated findings, such as a severe tuberculin reaction and the presence of the disease. The writer feels that the significance of lymphangitis with tuberculin reactions is to be considered from the standpoint of an infection with tuberculosis, which in children manifests itself as a glandular disease. The lymphatics are the distributors, and the phenomenon of lymphangitis speaks for an active tuberculous process. A glandular reaction following an injection of tuberculin is akin to a more pronounced skin reaction and is in turn an integral part of the most pronounced reaction, lymphangitis, which results from an active sensitization of the lymph channels to the products of the tubercle bacillus.

Serum Prophylaxis of Epidemic Parotitis.—REGAN (*Jour. Am. Med. Assn.*, 1925, 84, 279) immunized six groups of children, comprising 81 in all, exposed to epidemic parotitis at different times. He used an average injection of 3 cc of convalescent serum within a period varying from the first to the sixth day after exposure. Only 1 of these patients developed mumps, but 11 were discharged from observation before their possible incubation period was over, and the results in these 11 immunized patients are not known. The remaining 69 showed no evidence of the disease. The convalescent blood used for their immunization was taken from healthy adult donors, who were Wassermann negative and clinically free from any active signs of tuberculosis. The blood was collected between the extremes of the tenth and the twentieth day, usually the fourteenth or sixteenth day of their disease. It should be administered before the seventh day after exposure to

afford complete immunity. The possible value of the method of modifying the disease by injecting the serum late in the incubation and in somewhat larger doses may be of some use, and this may prove particularly advantageous in the prevention of orchitis.

Studies of the Salivary-urea Index in Children.—CALVIN and ISAACS (*Am. Jour. Dis. Child.*, 1925, 29, 70) determined the salivary-urea index in 196 children, the ages of whom ranged from two and a half to sixteen years. Eighty-five had normal urines; 111 had albuminuria, of which 10 had definite evidence of nephritis. Blood-urea determinations were made on 25 of these children, 3 of whom had normal urinary findings and 22 of whom had definite evidence of nephritis. The normal lower limit of the salivary-urea index in adults is 30. The salivary-urea index in this series generally averaged lower than the adult. The lowest index was 23, in a child of nine years. The highest was 50 and the average was 35. The age range apparently made little difference among the children studied, those above eight years averaging 35.8, and those below 8 averaging 34.8. Twenty-three of the total number of salivary indexes determined were below 30, and of these 13 patients had negative urines and 10 had some albuminuria. The lower trend of the figures in children corresponds to the generally accepted lower averages of normal blood urea, perhaps due to a lower protein intake. The relation of the level of the salivary-urea index to the protein content of the diet is being studied by the authors. The youngest child in this series was two and a half years of age. It was found too difficult to get the coöperation of younger children to complete the necessary chewing and expectoration. Several children were aged four years, and the oldest was sixteen years. Most of the children between three and six years coöperated readily, especially when the parent or nurse was near to watch the child and to encourage chewing and expectoration. Several children between the ages of three and eight years would not coöperate or were unable to understand what was wanted. In 2 cases in which coöperation was poor, and two hours elapsed before a sufficient quantity of saliva was collected, the salivary index was over 50, although the blood urea was normal. This can probably be accounted for by the autolytic changes in the saliva while standing. In 3 cases small amount of macroscopical blood from the gums was present in the saliva. This apparently did not change the index values, which varied from 36 to 48. In this series are included 111 children whose urine revealed albumin, varying from a trace to 4+; 99 with albumin from trace to 2+ and with no casts or occasional ones had a normal salivary-urea index; 2 others of this group had a high index, but had chewed for two hours as described above. Of the 10 children with definite marked nephritis, 4 had a normal salivary index, ranging from 34 to 38, and 6 showed a high index from 60 to 105, denoting urea retention, which was confirmed by blood-chemistry studies, the blood urea in the first 4 ranging from 15 to 24 mg., and in the last 6 from 58 to 110. The albuminurias of mild grade without evidence of serious kidney damage did not average any higher salivary index than did the normal cases. No patient showing a salivary-urea index below 50, on which a blood determination was done, showed a blood-urea value over the accepted

normal limit of 25 mg., and *vice versa*; the only children whose salivary index was over 50, and whose blood urea was normal, were the 2 who chewed for two hours, allowing autolysis to progress in the expectorated saliva. The 6 patients other than these 2, which had a high salivary-urea index over 50, had correspondingly high blood-urea values, and all were nephritics. The authors recommend the salivary-urea test in children because of the ease with which a specimen of saliva may be obtained.

Calcium and the Acid-alkali Balance.—HUMMEL (*Klin. Wchnschr.*, 1924, 3, 2384) shows that rickets and spasmophilia, although belonging clinically to the same group, have an opposite tendency in metabolism, the rickets being acidotic and the spasmophilia being alkalotic. The common point is the change connected with calcification of the bones. Calcium carbonate can be deposited from the bicarbonate only in an alkaline reaction. This reaction of the medium disappears when the calcium carbonate has precipitated. Since the process is reversible, high degrees of alkalinity occur if the precipitation of calcium carbonate is prevented. Calcified bones give an alkaline reaction, while the osteoid tissue is acid, as long as it is unable to take up lime. The gravest cases of rickets are not spasmophilic, because there are so many acid proteins of the osteoid tissues that the hydroxyl ions are easily saturated. A spasmophilic condition with its alkalosis is already a step toward the cure of the rickets.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Intracranial Bleeding in the Newborn.—SAENGER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, 65, 257) contributes a paper upon this subject from the clinic in Munich. He finds that intracranial bleeding in the newborn is very common. In 100 autopsies in 73 cases macroscopic evidences of bleeding were present. Of these, 46 had severe hemorrhage. Considerable bleeding developing during birth penetrates the subdural space and makes the subdural fluid blood stained. One cannot accurately distinguish between supratentorial and infratentorial bleeding. The cause of this accident is found in the simultaneous action of interference with fetal circulation during labor and the direct application of force in the delivery. The anatomy of the circulation is such that hemorrhage is frequently found in the right cranial sinus, as this is a point where an interruption in the circulation cannot occur without injury to the tissues. When congestion or prolonged interruption develops there is increased tension in the vessels which is communicated to the duplications of the dura, especially those above and below the large sinus bordering on the tentorium cerebelli. Clinical observation shows

that contracted pelvis, very strong labor pains, rigid birth canal, thin cranial bones in premature children and especially large children, are factors tending to this injury. Among methods of delivery manual extraction of the after-coming head and difficult forceps deliveries are especially dangerous. The mechanism of hemorrhage consists in pressure upon the flat bones of the cranium, producing a passive stretching of the duplications of the dura, accompanied by increased tension in the circulation. In studying these cases at autopsy, the circulation being injected, the point of hemorrhage can readily be found owing to the fact that the tissues retract. Particularly the longitudinal sinus and the veins of the tentorium are especially apt to bleed. The frequency and importance of these lesions, to which attention has already been called by others, are thus emphasized.

Placental Infarcts.—McNALLEY (*Am. Jour. Obst. and Gynec.*, 1924, 8, 186) has studied 1352 placentae with regard to the presence of white infarcts. He groups these infarcts in three classes. First are those which on close examination are found to be small masses of fibrin which have replaced a previous collection of blood. All the white infarcts on the fetal surface of the placenta belong to this class, as do many of the intraplacental and some of those seen on the maternal surface. They are not organized, but are caused by the laying-down of fibrin as a laminated clot. The second class is red in the beginning, but becomes white later. These may properly be called red infarcts. All large infarcts belong to this class and, in fact, most of those visible to the naked eye. These seem to be associated with the toxemia of pregnancy. The third class represent senile placental changes. A point of difference is found in the senile changes of the syncytium, which occur along with those in the bloodvessels and result in a deposition of fibrin about the periphery which cuts off the blood supply and produces necrosis.

The Use of Pituitary Extract in Obstetrics.—BURGUR (*Gynec. et Obst.*, 1924, 9, 136) describes his experiences in the Strasburg Clinic in the use of pituitary extract. He quotes the literature upon the subject, describes cases in which pituitrin acted well and states that he has used pituglandol in doses 1 cc and pituitrin in doses of 0.5 cc, as the intensity of the action is proportioned to the quantity injected. He gives small doses, one-half or one-third of the usual doses, repeated as often as necessary. The result of the drug should be obtained in a little less than an hour after it is given. It is rapidly eliminated so that one can repeat a dose in about an hour without danger. The number of doses given by various observers has reached, in one instance, twenty. He devotes considerable space to the accidents following the use of pituitrin, notably rupture of the uterus and has collected a large series of cases. He would use the drug at the end of the period of dilatation or, better still, conditions being favorable, during the period of expulsion. The presenting part must be well in the pelvis and there should be no retraction of the fetal part between pains. He believes that in most of these cases feeble uterine contraction indicates a spastic condition of the uterine muscle rather than exhaustion. He often combined a small dose of morphin with pituitary extract to reduce the element of spasm and violent uterine action. Cases of disproportion and pelvic contraction should be recognized by the general practitioner as complicated

and dangerous, and should be promptly referred to the hospital under the care of obstetricians. He urges that in cases where grave complications exist, due weight be given to these complications as well as to the administration of pituitrin in deciding the cause of an accident. Admitting that the improper use of pituitrin frequently causes fatal accidents, there may still be other factors in a given case which are of importance. It goes without saying, he remarks, that midwives should be strictly forbidden to use pituitary extract in any form. In skilful hands the drug may render valuable service and, equally, injury by improper administration. The writer urges that accidents in its use should be accurately described and published, so that the profession may learn the truth concerning this valuable substance.

Painless Child-birth by Synergistic Methods.—GWATHMEY (*Am. Jour. Obst. and Gynec.*, 1924, 8, 154) adds 200 to his 100 cases previously reported, treated by this method. He states that he has changed his formula nineteen times, but has made no alteration in the last 100 cases. At present this method is as follows: The patient receives from one to three hypodermics and one rectal instillation. The first hypodermic, $\frac{1}{2}$ grain morphin dissolved in 2 cc of a 50 per cent solution of magnesium sulphate, is given when labor is well established, pains four to five minutes apart, lasting thirty or more seconds. No more morphin is given, but by rectum there is administered a mixture of 2½ ounces of ether, 10 gr. of quinin hyprobromate in 2 drams of alcohol with enough olive oil to make 4 ounces. The doctor or nurse comes in contact with the patient often only twice; at most four times. The magnesium sulphate is in 2-cc ampules 50 per cent strong. If the first hypodermic has a marked effect, rectal treatment is given in one or two hours; if not, it is given within fifteen or twenty minutes. The effect of the combined treatment is usually seen with fifteen minutes and lasts about four hours. If needed, 2 cc 50 per cent magnesium sulphate are given hypodermically in addition once or twice. Noise is avoided as much as possible and the patient kept as quiet as possible. The author states that no method could possibly be safer or simpler, which is certainly an exhibition of sublime faith and self-confidence. Additional notes are given upon other methods, which serve to illustrate the perfection of that already described.

A Natural Immunity in the Newborn.—MUSSELMAN (*Am. Jour. Obst. and Gynec.*, 1924, 8, 45, 141) has studied this subject in the New Haven Clinic and quotes from the literature regarding it. It seems to be established that the human maternal serum has greater power to destroy bacteria than that of the newborn. This serum has a greater content of complement than that of the newborn. In maternal serum there is no parallel relationship between the condition of the serum of the mother and the child. Pregnancy itself does not cause an increase in the effectiveness of maternal serum. The difference is due to an actual deficiency in the serum of the newborn because it possesses an anti-complementary substance. Colostrum and milk have very little—if any—power to destroy bacteria. The power of serum as a germicide does not depend along upon its complement, but is greatly increased by it. These studies indicate that the infant is only partially, if at all, dependent upon its mother for antibodies or natural immunity.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Acute Ulceration of the Vulva.—Under this heading McDONAGH (*Brit. Jour. Dermat. and Syph.*, 1924, 36, 285) includes two clinical conditions: (1) Acute ulceration due to Doederlein's bacillus and (2) acute ulceration due to Vincent's organism which is frequently called *vulvitis erosiva et gangrenosa*. Both types of ulceration are rare and are due to organisms which are naturally saprophytic. An infection is caused only when the patient's general resistance is lowered or the local resistance has been damaged by uncleanliness, disease or trauma. These two clinical conditions are nonvenereal in nature and they are most prone to attack virgins. The author has not seen a case in a woman over thirty years of age. Both types of ulceration, especially in the former, may show a tendency to relapse. For the ulceration due to the Doederlein bacillus, or *Bacillus crassus*, there is no specific treatment, but the ulceration occasioned by the Vincent organism clears up rapidly under arsphenamin and relapses only when too many injections of this drug are prescribed. The form of ulceration due to the *Bacillus crassus* may be divided into two clinical types, of which the former is the more common: (1) Very acute, small and multiple ulcers, ushered in with rigors, fever, etc.; (2) less acute, larger and deeper ulcers unassociated with subjective symptoms. In the five cases of this type in this series there was no evidence of an erosion preceding the ulcer. The initial lesion appears to be an ulcer, which from the very beginning attacks the deeper tissue, hence the reason why the ulcers have a grayish-white appearance, and are covered with pus and stringy material, which is removed with difficulty. The most common sites to be involved are the inner surfaces of the labia. The ulcers are extremely painful, but there is little discharge and no lymphadenitis. The facts that the ulcers are not preceded by erosions, that they do not usually cause great destruction of tissue and that they do not emit a characteristic odor, serve to differentiate this form of ulceration from that occasioned by Vincent's organism. The acute ulceration due to Vincent's organism may occur *de novo* or appear as a superinfection, but is always ushered in with severe constitutional disturbances. There is often considerable discharge which gives off a very characteristic odor. The inguinal lymphatic glands are generally swollen and painful. The organism is easy to find and is not difficult to culture, the cultures also having a most offensive odor. In an incredibly short space of time a great destruction of tissue may occur. If the parts are left uncovered, exposed to the air and fre-

quently bathed with hydrogen peroxide the condition heals up, because the organism requires anaërobic conditions. Healing is expedited by two injections of arsphenamin, but if this number is exceeded the ulceration may relapse and spread with renewed vigor, clearly showing that treatment acts by stimulating the patient's resistance and not directly upon the microorganisms.

Clinical Study of Hypernephroma.—On reviewing the literature of hypernephroma, CUTLER (*Bull. Johns Hopkins Hosp.*, 1924, 35, 214) was struck by the scarcity of clinical data recorded relative to these tumors, although the pathology of these tumors has been carefully studied. He found that the occurrence of hypernephroma is comparatively rare, since at the Johns Hopkins Hospital there were only 32 cases which came to operation during a period of sixteen years, the average age of the patients being fifty-one years. The condition is practically twice as common in the male as in the female. The average duration of symptoms from the time of appearance of the first symptom to the time of operation in this series was three and a half years. Hematuria is by far the commonest symptom of the disease, being rarely absent and in half of the cases it is the initial symptom. Pain was the second commonest symptom and is usually a localized soreness or discomfort in the kidney region, and is quite distinct from the pain associated with renal colic. Renal colic occurred in 20 of the 30 cases in which its presence or absence was mentioned. In the majority of instances the pain was associated with the passage of long, wormlike blood clots and the colic was undoubtedly due to blocking of the urinary passages by these clots as the pain was relieved immediately after the clots were passed. Dysuria and retention were present in 7 of the 32 cases. When hemorrhage from the tumor was sufficiently extensive blood clots formed, which by filling the bladder produced a marked dysuria and retention. Frequency of urination was present in only 4 of the cases, thus this symptom is rare in this condition as compared to its frequency in tumors of the bladder. Hematuria, on the other hand is a common initial manifestation in both conditions, therefore the presence or absence of frequency of urination in a patient complaining of hematuria may serve as a useful differential point in the history between the two conditions. A tumor mass is usually palpable and it is not at all uncommon to have renal calculi associated. Regarding all temperatures of 99° or over as febrile, this series showed 75 per cent of the cases to be febrile although the elevation of temperature was rarely over 100°. The phenolsulphonaphthalein test shows a marked decrease in excretion on the diseased side and pyelography has been of very great help in the diagnosis of kidney tumors, the majority, but not all, of the kidney tumors producing markedly noticeable distortion of the kidney pelvis.

Operative Cure of Pruritus Ani and Vulvæ.—One of the most annoying and refractory conditions which the gynecologist is called upon to treat is the intense vulvar and anal itching, for which no cause can be found. ALLEN (*New Orleans Med. and Surg. Jour.*, 1924, 76, 532) again describes his method of treating these cases which has been quite satisfactory in practically every case on which it was tried.

The operation consists of the separation of the skin from the underlying tissue, thus dividing all nerves which reach the affected parts, rendering these parts anesthetic and preventing the skin from immediately healing to the underlying tissues by packing, which is kept up until a firm bed of granulation has formed, which usually requires about one week. When the packing is discontinued the skin is allowed to fall back into place, where it soon is again firmly united, leaving an anesthetic area which nearly equals the extent of the undermined area, which gradually diminishes in size, but is not followed by a return of the pruritus. The operation on the anal region is the simpler. The area involved must first be accurately determined and then a series of incisions is made beginning at the anal margin and continuing outward to about $\frac{1}{2}$ inch beyond the affected area, which rarely exceeds 2 inches. These incisions are made about 1 inch apart at their peripheral extremities until the entire peri-anal region has been covered. These skin strips are now dissected up, preferably with a scalpel, except at their two ends, which are left attached. In separating the skin from the subcutaneous tissues, a small margin of tissue is left attached to its under surface to insure sufficient circulation to prevent sloughing. As the pruritic area rarely involves the mucous surfaces, the incisions need not invade them. The space beneath the flaps is packed with gauze as described above and frequent sitz baths, with a liberal supply of soap, are insisted on as after-treatment. The packs may need changing, but often remain *in situ* for the full period of one week. The operation sounds logical, and the author is so enthusiastic about it that it would be well to bear it in mind when we are called upon to treat this distressing condition.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

Hearing in the Presence of a Noise.—Many deaf persons, with middle ear trouble, say that they "can hear better in a noise," this noise being the noise of a street car, an elevated train, a machine shop or some similar type of disturbance. The observations which have been actually made seem to be based on the fact that these persons can carry on a conversation with a normal hearing person more easily in a noise than otherwise. KRANZ (*Ann. Otol., Rhinol. and Laryngol.*, 1924, 33, 283) conducted a number of tests on this type of deafness by talking to the subject in a monotone, repeating over and over some phrase and either (1) using a telephone receiver which was emitting a loud tone of 120 cycles per second and alternately placing it near to his ear (1 to 3 inches) and taking it away, or (2) using a specially

designed bone-conduction type of telephone receiver actuated by a 120-cycle current and alternately placing this on his head and taking it off, there being sufficient intensity to give the person a loud subjective sound when on his head. By these procedures it was learned that the presence of the disturbance caused by either the bone or air conducted sound did not in any case result in any improvement in the subject's ability to hear or to understand the phrases being spoken. The author states that, seemingly, the determining factor in the ability of some deaf persons to converse better in a noise than otherwise is undoubtedly the increased loudness with which a normal person talks in the presence of a noise. The normal person, of course, tries to talk so that the sound of his voice will predominate over the disturbing noise as judged by his own hearing. The actual ratio of the objective intensities of the speech and the disturbing noise striking the ear is the same for the normal and the deaf individual, but due to the difference in the acuity of the two persons the speech sound will for the deaf person be much farther above the low limit of audition as compared with the disturbing noise than will be the case for the normal person. Another factor is the difference in frequency between sounds concerned in speech and those of noise. The latter are probably of much lower frequency than the former, and it is also a fact that people with middle-ear trouble are particularly deaf at low frequencies. The noise bothers the deaf person less than it does the normal person.

The Tympanic Presclerosis of Citelli.—As reviewed by CALDERIN (*Rev. españ. de. laringol.*, Madrid, 1924, 25, 220) this condition, which affects for the most part older children but also infants, is important inasmuch as it indicates impending otosclerosis. Occurring in those with adenoids, it is seen particularly in cases who have further impairment of audition following adenoidectomy. In many instances a familial history of otosclerosis can be elicited and divers constitutional defects are present. Higher tones are heard better than lower tones. Air conduction is diminished. Normal mobility of the ossicular chain obtains; the Eustachian tube is patulous and local findings fail to account for the impaired hearing, which would seem to result from changes in the bones around the tympanic cavity and labyrinth. As with so many other states, cure depends on early diagnosis and treatment. As suggested by Citelli, calcium in combination with preparations of iodine and peptone provide efficient therapeutic measures.

Bacteriologic Study of Middle-ear Infections.—VALENTINE (*Jour. Infect. Dis.*, 1924, 35, 177) conducted a series of investigations in cases of acute and chronic otitis media to ascertain: (1) The relative frequency of the different bacterial varieties; (2) the bacterial flora of the aural discharge in acute cases at intervals over a considerable period of time; (3) the throat flora in acute respiratory infections prior to development of an ear condition in order to trace bacteriologically the source of the otitic infection; (4) the throat flora in all cases of otitis media at the time of the original paracentesis and also later to determine whether the anatomical, clinical and bacteriological picture of the throat had any relation to the severity and subsequent history of the ear condition; (5) the bacterial variety found in the majority

of acute cases to learn if there was a specific serological variety which had a peculiar affinity for an elective localization in the ear; (6) the ultimate condition of chronicity or deafness in the acute cases from the standpoint of the original bacterium found in the ear infection (the relation of the different varieties of secondary invaders to the final condition of chronicity). Extensive and detailed observations were recorded on 100 acutely infected middle ears in 77 cases and on the aural discharge from 12 chronic cases. It was found that the beta-hemolytic streptococcus was the microorganism most frequently encountered, occurring in 53 per cent of the acute cases, while staphylococcus was encountered alone or with other bacteria in about 30 per cent. Pneumococci, green streptococci and diphtheroid bacilli predominated in a small percentage of cases. In the chronic group diphtheroid bacilli, staphylococci, *Bacillus pyocyaneus*, *Bacillus proteus* and *Bacillus coli* were obtained in pure or mixed culture. In those cases in which hemolytic or green streptococci or pneumococci were found the same bacterial species were also found in the throat. In 9 cases studied the *same serological* variety of streptococcus were present in the throat and the *ear discharge*. In most cases cultures made from the aural discharge several days or a week after paracentesis showed that the apparent etiological bacterium had become reduced in number, while the proportion of the other varieties had increased. In 19 out of 22 cases of bilateral otitis media, involved at approximately the same time, the same bacterial species were obtained in the primary culture from both ears in each individual. The heterogeneity of the strains isolated from the majority of acute middle-ear infections indicated the absence of a common primary or secondary causative agent. In the cases studied over a considerable period of time diphtheroid bacilli and staphylococci were found to be the most frequent secondary invaders in the ear discharges after the acute stage of the infection. There was some indication that in certain cases these bacterial varieties may have been factors responsible for the chronicity of the inflammatory process. The authoress concluded by saying that "The presence of numerous serological varieties of beta-hemolytic streptococci as the apparent etiological organisms in a series of middle-ear infections indicates that the use of a stock streptococcus vaccine is probably of little or no specific value. However, an autogenous vaccine made from the original variety in the ear discharge should be tried."

The Etiology of Ozena.—NASSO and TASSI (*Pediatrics*, 1924, 32, 1065) succeeded in isolating from the filtrate of crusts and nasal secretions of 24 persons, with ozena, a tiny, nonmotile, Gram-positive microorganism. This bacterium could be cultivated, both aerobically and anaerobically in catalyzing mediums of the Tarozzi-Noguchi type. When inoculated into rabbits—either intravenously or locally in the nasal submucosa, the organism produced a condition characterized by mucopurulent secretion, crust formation and abnormal widening of the nasal fossæ. A bacterium, identical with that injected, could be recovered from the filtrate of the nasal secretion of the inoculated rabbits. In the blood serum of individuals suffering with ozena, as well as of the experimentally infected animals, specific agglutinin and amboceptors for the microorganism could be demonstrated.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

ASSISTANT PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

A Case of Early Cancer Arising from Ulcer of Stomach.—Moszkowicz (*Virchows Archiv*, 1924, 253, 511) reports the finding of a small ulcer along the lesser curvature of the stomach, which showed the typical characters of the common peptic ulcer. In the routine examination of this specimen the surgical diagnosis was substantiated. Only upon more minute analysis and further serial section of the ulcer was a small cancerous invasion discovered along one border of the ulcer. This tumor showed colloid degeneration and the cells composing it formed tubular structure different from the normal neighboring mucosa which it undermined and displaced. Occasional small islands of aberrant epithelial masses were also found in the deeper portions of the stomach wall where the atypical characters were still more pronounced. The author is convinced that he is dealing with a true cancer of early development, and arising in an old gastric ulcer. The case illustrates well the care which must be taken in examining gastric ulcer to exclude the possibility of cancerous growth in the tissues.

Spontaneous Rupture of the Aorta.—LETTERER (*Virchows Archiv*, 1924, 253, 534) reports 2 cases of young individuals in whom rupture of the aorta had occurred. Both were men, aged thirty-nine and twenty-eight years, respectively. In one of them there was a history of injury, the individual falling from a height during athletic exercises. In the other case the individual gave a history of handling heavy boxes although no direct relation between his work and the injury could be traced. The rupture of the aorta in one took place immediately above the aortic ring and in the other in the descending arch. In both instances the tears were clean cut and the author was unable to find any local lesion in the wall to account for unusual weakness. Marked hypertrophy of the heart and peripheral arteriosclerosis was present in the 1 case but absent in the other. The history in both cases is too indefinite to account for the rupture, and the absence of changes in the aortic wall gives no clue for the localization of the injury. The aorta showed no constriction above the entrance of the ductus arteriosus. The author believes that two main factors play a part in the rupture: (1) Sudden increase in blood pressure, and (2) tugging of the heart through compression or distortion of the body.

Lipoid Analyses in the Adrenals of Cattle.—SORG and JAFFE (*Centralbl. f. allgem. Path.*, 1924, 35, 353) undertook a histochemical analysis of the adrenals of both male and female animals and found that they were unable to isolate cholesterolester or any of the cholesterin

compounds but, on the other hand, varying quantities of lipoids were distinguishable. These results have been repeatedly verified in the microchemical analyses of various investigators. Chemical extraction showed the presence of small quantities of cholesterol. Somewhat similar results were obtained in the analysis of corpora lutea. The lipoids in the adrenals are similar to those found in the sex glands. The chemical characters of the content of these various tissues is very similar and the small quantities of cholesterol which could be isolated from them was found to be in the free and not the combined state. They believe that these small quantities of cholesterol are the results of a cell disintegration rather than cell metabolism. They come to the conclusion that combined cholesterol plays no part in cattle in the metabolism of lipoids.

The Production of an Exotoxin by Certain Strains of Staphylococcus Aureus.—Dick and Dick's demonstration of a dermatotoxic poison from scarlet fever strains of streptococcus hemolyticus prompted PARKER (*Jour. Exp. Med.*, 1924, 40, 761) to search for a similar poison in Staphylococcus aureus. She succeeded in demonstrating in sterile filtrates of broth cultures of certain strains of Staphylococcus aureus, a powerful poison with a selective action for the skin. The relationship of this poison with leukocidins was not investigated. Four out of twenty-one strains showed the poison, the work being carried out on rabbits. One of the rabbit-negative strains produced an effect in the human skin similar to the Dick reaction. The medium used was a well-buffered broth solution containing a small amount of glucose. The presence of glucose (or probably the acids resulting from its breakdown) had an inhibiting effect on poison production. The toxin could be demonstrated in sterile Berkefeld filtrates of twenty-four hour cultures but the most toxic poisons were obtained after four to six days' growth. The toxicity of filtrates was tested by intracutaneous and subcutaneous inoculation, all inoculations being controlled. The reaction, which is described in detail, was always characteristic and systemic toxic symptoms were observed. The histological changes in the skin reactions are reported. Intravenous injection of the poison was tried but irregular results were obtained. The toxin studied seemed to be identical from all strains, was definitely thermolabile and produced an antitoxin which was not present in the sera of normal rabbits. This antitoxin was produced in very small quantities if at all, in using the intravenous route of immunization. The work is still being carried on and further communications on this interesting study may be looked for.

The Complement-fixation Test in Tuberculosis.—A comprehensive survey of the previous work done and the conclusions reached is given by WILLIAMS and BRYCE (*Jour. Path. and Bact.*, 1924, 28, 401). Following this they outline the standard that must be attained before the test can be made use of diagnostically. They base their observations and conclusions on the examination of over fifteen months. The technic used was that described by Harrison for the Wassermann test. Various antigens were used, the details of which are given. Three groups of sera were used. The first from proved cases of tuberculosis, the presence of bacilli in sputum, urine, tissues, or guinea pigs being accepted as

proof. These cases gave 74.4 per cent of positive results. The second group was from a few healthy adults and from a large number of hospital patients in whom there was no reason to suspect tuberculosis. Five per cent of these gave positive results and in all but one of these it was impossible to exclude the possibility of tuberculosis. In this connection, the authors examined a series of 500 individuals, which included many of the foregoing group, for skin allergy, 66.6 per cent were found to react positively to the von Pirquet test. Their explanation of the difference in the results of the tests is the assumption that the complement-fixation reactions indicate active disease rather than previous infection and that those giving positive von Pirquet reactions have been at some time infected and have been able to resist it. They consider that this does not weigh against the specificity of the test. The last group was of clinically certain tuberculosis where aid in diagnosis was lacking, and of suspected tuberculosis where aid in diagnosis was sought. Of these 50 per cent of pulmonary cases, 18.5 per cent of bone cases and 40 per cent of a heterogeneous series gave positive complement-fixation results. The fact that no bovine strain was present in the antigen may explain certain negative results. From their study they conclude that the test is specific but that it is not completely satisfactory as a diagnostic agent. While a negative result does not exclude tuberculosis, a strongly positive reaction is, with few exceptions, evidence of the disease in an active form. Finally, the routine performance of the Wassermann test simultaneously with it draws attention to the possibility of a syphilitic basis for the lesions present in some cases suspected of being tuberculous.

The Differentiation of Two Distinct Types of Phagocytic Cells in the Spleen of the Rabbit.—CUNNINGHAM, SABIN and DOAN (*Proc. Soc. Exp. Biol. and Med.*, 1924, 21, 179) anesthetized a rabbit and exposed the spleen. By splenic puncture blood and tissue cells were obtained and studied in supravital films with neutral red and Janus green staining. Two types of phagocytic cells were found: (1) Monocytes of the circulating blood and (2) macrophages, histiocytes or clasmatocytes, the former forming 17 per cent of the splenic cells and the latter 1 per cent. The clasmatocytes are large cells with relatively small oval nuclei, located toward the periphery of the cells. They react intensely to neutral red and the aggregations of the stain are scattered irregularly throughout the cytoplasm. They contain a few or no mitochondria. The monocytes are somewhat smaller in size with relatively larger, horse-shoe, or kidney-shaped nuclei. There is a clear space in the cytoplasm surrounded by a rosette of small, radiating aggregations of neutral red. Mitochondria are always present and are brilliantly stained with Janus green. The pattern of the monocytes is quite specific and is only occasionally obscured when the cells are in active motion. Both types of cells are phagocytic for red blood corpuscles. When a corpuscle is ingested by a monocyte it is placed in the periphery of the rosette of neutral red granules without disturbing the arrangement. But in the clasmatocyte such a corpuscle is placed adjacent to the nucleus on the side having the most cytoplasm. The monocyte arises from a "stem cell" of mesenchymal origin in the pulp, where there is no endothelium whatever; while the clasmatocyte arises from the endothelium of the sinuses.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Incidence of Certain Communicable Diseases Common among Children.—COLLINS (*Pub. Health Rep.*, 1924, 39, 1553) summarizes his studies based on observations of school children as follows: "In the course of certain studies in child hygiene, information was obtained from approximately 35,000 school children from five to nineteen years of age as to whether they had ever had measles, whooping cough, mumps, chicken pox, scarlet fever, or diphtheria. The children were classified according to age, sex, color, and nativity or nativity of the parents. The curves of the percentage of children who had had an attack of these diseases at some time in their lives rises fairly rapidly as age increases until about the thirteenth or fourteenth year, after which time the rise is very slow, except in the case of mumps, which continues to rise considerable through the nineteenth year. The slackening in the rate of increase presumably means that the susceptible material is largely used up. When the annual incidence was considered it was found that for the ages studied the maximum incidence of measles was at six to seven years; whooping cough, five to six years; mumps, seven to nine years; chicken pox, five to six years; scarlet fever, eight to ten years; and diphtheria, five to seven years. As age increases, within the limits of those included in this study, the annual incidence rapidly declines. By the time the adult ages were reached, about 89 per cent of the children had had measles, about 78 per cent had had whooping cough, 65 per cent mumps, 52 per cent chicken pox, 12 per cent scarlet fever, and 9 per cent diphtheria. Measles, whooping cough, chicken pox, and scarlet fever seem to have been more prevalent among girls than among boys. The rates for mumps and diphtheria are about the same for the two sexes. Measles, whooping cough, mumps, and chicken pox seem to have been more prevalent among the native white than among the foreign children. The rates for scarlet fever and diphtheria seem to be about the same for the two groups. Measles, chicken pox, scarlet fever, and diphtheria seem to have been more prevalent among the white than among the colored. The rates for mumps were possibly higher among the colored. Whooping cough seemed to be about the same in both groups."

Per Capita Medicinal Requirements of Narcotics.—DuMEZ (*Pub. Health Rep.*, 1924, 39, 2358-2360) endeavored to ascertain, by visiting physicians, dentists, pharmacists, and so forth, the legitimate requirements for opium and coca leaves for a population of about 70,000.

Reducing the figures to a per capita basis it was found that 6.98 grains of opium were sold and 29.32 grains of coca leaves. This indicates that for the United States 105,697 pounds of opium and 443,988 pounds of coca leaves would be required per year.

Mortality from Malaria.—MAXCY (*Pub. Health Rep.*, 1924, 39, 2559-2561) has studied the mortality from malaria in the southern states and finds in general a sustained decrease and considers that the evidence pointing to the gradual disappearance of the disease is encouraging.

Plague.—The Public Health Service.—(*Pub. Health Rep.*, 1925, 40, 51) reviews the history of plague, with special reference to the present pandemic. It is pointed out that nothing short of interference that would paralyze commerce will eliminate the risk of the spread of the disease on vessels. Rat infection in cities may require many years for eradication. Even the pneumonic form is traceable eventually to rodents. The necessity for rat-proof buildings is pointed out and the statement made that the rat must be built out of existence. The recent outbreak of plague, both pneumonia and bubonic, in Los Angeles (*Pub. Health Rep.*, 1925, 40, 191) has brought to the front the fact that we have in the United States an endemic form of rodent plague which signifies the necessity for a persistent campaign. The spread of plague foci is regarded as of greater significance and it is pointed out that these have increased in the last half-century so that no longer may we regard as menaces only the remote classic foci in Asia and Africa. The world distribution is given for a period of years and special stress is laid on seasonal prevalence.

Rocky Mountain Spotted Fever: Non-filterability of Tick and Blood Virus.—SPENCER and PARKER (*Pub. Health Rep.*, 1924, 39, 3251-3255) give the following summary: (1) The virus of Rocky Mountain spotted fever as it occurs in the blood of guinea pigs and in emulsions of infected tick viscera (adults and nymphs) will not pass Berkefeld "N" and "V" filters. (2) Inoculation of filtrates of blood or tick virus does not produce immunity in guinea pigs. (3) The coarse "V" filters that hold back the virus of Rocky Mountain spotted fever will readily pass broth cultures of *Staphylococcus aureus*. (4) The failure of the virus to pass Berkefeld filters does not appear to be due to a chemical affinity for or adsorptive property of the material of which the filter candles are made.

A Study of the Pellagra-preventive Action of Dried Beans, Casein, Dried Milk, and Brewers' Yeast, with a Consideration of the Essential Preventive Factors Involved.—GOLDBERGER and TANNER (*Pub. Health Rep.*, 1925, 40, 55-78) review some phases of their studies on pellagra which throw fundamental light on an obscure corner of etiology. The following elements of diet are considered: Soy beans and California black-eye peas were inadequate to prevent pellagra. Casein appeared to have a good effect on general nutrition and prevented or delayed the development of the dermatitis; it failed, however, to prevent some of the other symptoms and signs of the disease. Dried skim milk seems to have some pellagra-preventive action. Brewers' yeast appeared to be of great value in preventing the disease. The following conclusions are

drawn: (a) A liberal supply of protein, presumably of good biological quality, does not completely prevent, though it may modify, the clinical picture of pellagra by notably delaying or preventing the development of the distinctive dermatitis. This modifying action may be of an indirect, sparing nature. (b) In the prevention (and presumably causation) of pellagra there is concerned a heretofore unrecognized or unappreciated dietary factor which we designate as factor *P-P*. This may be effective with but little, possibly without any, coöperation from the protein factor. (c) Factor *P-P* may possibly play the sole essential role in prevention (and causation) of pellagra. (d) Factor *P-P* is present in brewers' yeast, in milk and (on the basis of our experience with fresh meat) in lean beef; it is very low, or lacking, in dry soy beans, dry cowpeas, butter, cod-liver oil and canned tomatoes.

The Epidemic Outbreak in Japan.—SYDENSTRICKER (*Pub. Health Rep.*, 1924, 39, 3215-3219) presents the available data on an apparently hitherto unrecognized disease having points of similarity to epidemic poliomyelitis, lethargic encephalitis and cerebrospinal meningitis. The epidemic was explosive in nature and lasted three or four months, beginning in July. The disease appears to be slightly or not at all contagious. The onset of temperature is sudden and the fever may go to 41° C.; nausea, vomiting and insomnia may occur. The temperature reaches normal in from about eight to fifteen days. There is a spastic condition of upper and lower extremities and strongly marked Kernig sign; no Babinski nor Oppenheim sign. Pulse is slow in relation to the temperature. Unconsciousness or deep somnolence is a predominant symptom; in severe cases coma occurs, sometimes delirium. Petechial hemorrhages have been noted on the backs of patients. The only laboratory findings of note are a spinal fluid cell count of 10 to 40 and a marked increase in polymorphonuclear neutrophils. At autopsy there is congestion and edema of meninges and parenchymatous degeneration of liver and kidneys. Cultures were negative. The disease was reproduced in rabbits by subdural injection of filtrates.

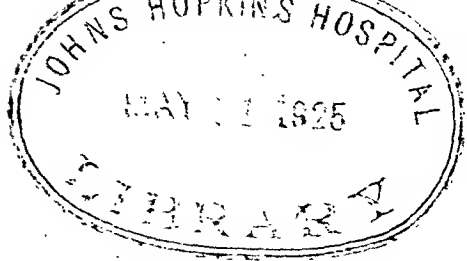
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ORIGINAL ARTICLES.

CARCINOMA AND SARCOMA OF THE ESOPHAGUS:
A PLEA FOR EARLY DIAGNOSIS.

BY CHEVALIER JACKSON, M.D., Sc.D.

(From the Bronchoscopic Clinic, Philadelphia.)

MALIGNANT disease of the esophagus with its 100 per cent mortality is one of the greatest reproaches to surgery today. In almost all other fields at least a few cases are cured. While I cannot bring forward a method of cure, I can, I think, show why the surgeon has never had a fair chance to attempt the cure of these wretched sufferers inevitably and invariably doomed to a slow and painful death.

In every form of visceral cancer the surgeon never had a chance to obtain curative results of value until there were developed reliable means of affording a positive diagnosis before it could be made by the classic "history of the case, pain, hemorrhage, emaciation and cachexia." Surgical treatment of cancer of the esophagus is still floundering in this slough of despond, notwithstanding the fact that a means of diagnosis is available by which an endoesophageal cancer no larger than a pea can be diagnosticated with a certainty that is as close an approach to infallibility as anything known to medical science.

The reason for this sad state of affairs is that the textbooks and most of the journal articles still ignore or slight the only early means of diagnosis and advocate exclusively or chiefly the methods of diagnosis that are *always negative in the early stages of the disease*. How, under these circumstances, is a surgeon ever to have a chance to deal with the disease in the early stages?

The ultimate history of nearly every case of cancer of the esophagus shows it to have been classed as a medical case until the patient was moribund from food and water starvation, cachexia, metastases and suffering. Then the surgeon was called in to do a gastrostomy on a dying man. Naturally the surgeon is not very enthusiastic over the results obtainable by gastrostomy on such a patient; and it is hopeless for him to try to develop a curative operation which of necessity is a major one, on such clinical material.

The responsibility for this state of affairs rests not upon the practitioner, nor upon the internist, nor the surgeon, but rather upon the general failure to recognize the fact that, while esophagoscopy is a rapid, safe and almost infallible means of making a diagnosis, it is so only in the hands of those who have sacrificed the time necessary to master the few but essential details of its technic. In the hands of the untaught, esophagoscopy is a dangerous and misleading means of diagnosis. The fault then is that too few men have considered it necessary or worth while to learn how to do esophagoscopy, and especially how to avoid the serious and fatal complications that are sure to follow, in a certain percentage of cases, the uninstructed attempts to pass the esophagoscope.

Blame for previous lack of courage to urge the need for training before attempting esophagoscopy rests heavily upon the author.

Etiology, Incidence and Location. *Irritation and Preëxistent Disease.* This is not the place to discuss the unsettled question of the etiology of cancer in general. It is conceded that irritation can be a factor in the localization if not in the actual cause of cancer (Coplin,²⁹ Ewing⁵ and others). The irritations peculiar to the esophagus are: (a) Those incidental to the passage, or; (b) stagnation of foods, and to the (c) regurgitation of the acid contents of the stomach. Our statistics show a preponderance of cancers at the lower end of the esophagus, which is the region most subject to irritation by all three of these factors. Statistics of cases in Scotland and in China, as pointed out by A. Logan Turner,¹ J. S. Fraser,² W. T. Gardiner³ and G. Ewart Martin,⁴ show a preponderance (2 to 1) of cancers in the upper third, and especially in the postericoidal region, some indeed involving the hypopharynx. This preponderance is regarded by the authors referred to as possibly caused by the drinking of excessively hot tea by women of the working classes. This is especially striking because the total incidence of cancer of the esophagus shows relative rarity in women. The high cancers of the esophagus in China referred to by some authors as due to the eating of excessively hot rice is a very important observation, but is not quite so striking because of the preponderance in men; but there seems to us little doubt that the relative insensitiveness of the esophagus to hot food or drink exposes it to injury from this cause in persons who have learned the trick of get-

ting the hot food or drink past the relatively very sensitive anterior portion of the tongue.

One factor in irritation is stagnation. The esophagus normally empties itself downward without delay. If this is interfered with it tries to empty itself upward by regurgitation. Unlike the stomach, continued contact of food is abnormal and irritating. When to this are added the irritants quickly developed by fermentation of the stagnant food, we have an extreme degree of irritation that results in congestion and chronic esophagitis, as observed with the esophagoscope in hundreds of cases. While we have abundant esophagosopic evidence of this static esophagitis and irritation as a factor in increasing the degree of stenosis and the rapidity of growth of cancer, our records do not indicate precancerous stenosis as a cause of cancer, certainly not as a frequent cause. Only about 5 per cent of our cases gave a history indicating any delay in swallowing prior to what might be considered the onset of the cancerous obstruction. The 5 per cent of cases in which a preceding stenosis was probable includes cases of lye burns, pulsion diverticulum, probable luetic stenosis, probable spasmodic stenosis and preventriculosis (so-called "cardiospasm"). In 2 cases histologically proven and ultimately fatal, cancer developed at the edge of a pulsion diverticulum. It thence descended into the esophagus in 1 case; the other was not esophagoscoped later, but may have extended in the same direction. In 3 other cases the history and enormous diffuse dilatation indicated a preventriculosis (so-called "cardiospasm") as a predecessor of adenocarcinoma at the hiatal level. In making deductions as to preëxisting stenotic disease, it is well to include only cases in which there remains objective evidence of the preëxisting lesion. Esophageal cancer, if free from the synergistic starvation, badly balanced diet and local irritation, is a disease of slow progress. We have had cases survive as long as five and six years.

Our statistics approximately agree with those of practically all other observers in the preponderance of cancer at the normal points of narrowing, the cervical portion, the crossing of the left bronchus and the hiatal level. The region of the crossing of the left bronchus is often referred to as the level of the aortic arch or the bifurcation of the trachea. The physiologic narrowing in this region, however, corresponds to the crossing of the left bronchus, as observed at esophagoscopy, which is the only reliable means of getting such anatomic data in the living. The left bronchus presses toward the spine; the aorta at a slightly higher level displaces sidewise toward the soft tissues. No fault can be found with the theory that these narrowings expose the mucosa to greater irritation than the intervening portions, and the clinical history of cancer almost everywhere in the body shows a predilection for sites particularly exposed to irritation (Coplin,²⁹ Ewing⁵).

In sarcoma, especially lymphosarcoma, long-continued irritation and chronic irritation are conceded causes; but our 3 cases of sarcoma of the esophagus afford no evidence as to etiology. The lesion in 1 case of lymphosarcoma was not primary in the esophagus.

Age is undoubtedly an etiologic factor. Our youngest patient with cancer of the esophagus was nineteen years old, another patient was twenty-six years old; all the others were over thirty. About 75 per cent of the patients were between forty and sixty years of age, the sixth decade of life being the most susceptible. Our youngest patient with sarcoma of the esophagus was a boy, aged six years; another patient was thirty-two years; one patient with lymphosarcoma was aged forty-three years, the other, sixteen years.

Sex should be considered perhaps rather a cause of location than a fundamental factor in etiology, because the total incidence of cancer in the two sexes is not far from equal. The difference of cancer incidence in the esophagus in the sexes is very striking. In our cases men preponderate in the proportion of almost 9 to 1 (87 + per cent). The statistics of A. Logan Turner¹ show a preponderance of women, approximately 2 to 1. This preponderance of women, as pointed out by A. Logan Turner and J. S. Fraser,² may be related to the fact that the cancers were chiefly among women of a class who drink frequently of tea excessively hot, a habit not prevalent among men in the same region. Viewed in this light the large incidence in women is not directly a matter of sex. The converse is true in China, where excessively hot rice is eaten by the men (Fraser²).

Anomaly. In 1 of our cases we found a fistulous tract lined with apparently normal epithelium, situated about 2 cm. proximally from the upper border of the growth, in the middle third of the esophagus. Whether there was any etiologic relationship or not, we of course cannot say. The fistula seemed blind at its lower end on insertion of a fine forceps closed; no lower orifice could be demonstrated.

In 2 of our cases of histologically proven cancer the sections showed mucous glands similar to those normally present in the gastric mucosa. These embryonal errors may have been factors in the etiology of the malignant lesion by an inherent low resistance. It is more likely, however, that, as stated by James Ewing,⁵ "the sudden transition of epithelial types which they present offers a predisposing factor for epithelioma." In this connection it is interesting to note that of 16 cases of peptic ulcer of the esophagus at the Bronchoscopic Clinic, 6 were associated with the gastric glandular type of mucosa, as elsewhere reported.

Pathology. Type of Growth. In 671 cases in which a specimen was taken and reported upon as malignant the types of growth found were as follows:

Squamous-celled and atypical epithelioma	337
Basal-celled	2
Adenocarcinoma	316
Lymphosarcoma	2
Round-celled sarcoma	2
Fibrosarcoma (epithelioma developing on scar?)	1
Squamous-celled, plus gumma	1
Squamous-celled, plus tuberculosis	1
Mixed, type uncertain	2
Ulceration but probably malignant	7

The foregoing does not include cases in which the specimen was reported negatively for malignancy, because in no such case did the progress, or any other phase of the case justify its inclusion in a list of malignant cases. The adenocarcinomatous type of growth was located in the lower third in almost all the cases. The squamous-celled type was found at all levels, but chiefly in the upper two-thirds.

Sarcoma of the esophagus has been observed 4 times at the Bronchoscopic Clinic. One of these cases has already been reported.⁶

Mixed Lesions. That tuberculous, luetic and cancerous processes can be combined in a mixed lesion in the esophagus, though rarely, has been established. That any 2 of the 3 may be combined has also been established and is less rare than the triple combination. For an excellent review of this subject, with a comprehensive bibliography and the complete report of a well-studied case, the reader is referred to the article by L. W. Dean.⁷ Our statistics show a combined lesion of lues with cancer and of tuberculosis with cancer, but not of all 3 in one lesion in the esophagus.

In 14 of our cases of histologically proven cancer a strongly positive Wassermann reaction was obtained: All of these patients had dysphagia. Antiluetic treatment improved the ability to swallow in 10 of the patients, but as gastrostomy was done in 4 and in all the others the diet was regulated to prevent stagnation by eliminating milk and solids, the improvement cannot be taken as conclusive evidence of a luetic lesion of the esophagus. In 1 case, however, the diminution of a large mucosa-covered nodular mass on the left wall (10, Plate II), as seen esophagoscopically after two months of saturation with mercury (11, Plate II), corroborated the diagnosis of a combined luetic and cancerous lesion. This patient ultimately died of cancer.

In another of the cases with a strongly positive Wassermann reaction the histologic examination by Dr. Ernest W. Willets showed, in addition to a typical squamous-celled cancerous process, in an adjacent portion of the specimen of tissue, free from epithelial infiltration, the vascular changes usually associated with lues and necrotic tissue suggestive of gumma. No spirochetes or bacilli could be demonstrated. Tuberculosis could not be excluded histologically, but no clinically demonstrable tuberculous process existed elsewhere in this patient. It seemed justifiable to consider

this case one of combined lues and cancer of the esophagus. He died ultimately of what was reported by his physician to be salvarsan poisoning.

In a third case of strongly positive Wassermann esophagoscopy showed a reappearing purulent discharge from a fistulous opening with a mass of granulations at the margin. Tissue removed from this granulating area, examined histologically by Dr. Ernest W. Willetts, showed typically tuberculous elements, though no bacilli were demonstrable in the tissue. One week later another esophagoscopy was done. A small tube (7 mm.) was used to pass the suppurating area. The lower margin of the lesion was found bleeding freely from a granular area, from which a second specimen was taken. The esophagus at this point was tightly strictured by a firm infiltration of the entire wall. The second specimen removed showed typical squamous-celled epithelioma. This patient had an advanced pulmonary tuberculosis with an abundant positive sputum. This was undoubtedly a combined tuberculous and cancerous lesion, though which was primary it is impossible to say.

In a fourth case, with strongly positive Wassermann, a squamous-celled epithelioma was found with a scar at its margin. Whether or not the scar was a cicatrized luetic lesion could not be determined. There was no history of swallowing a corrosive nor of difficulty in deglutition. The primary luetic lesion dated back twenty years. There was a small sacculated aortic aneurysm; the lungs were normal.

In 2 other cases in which a diagnosis of pulmonary tuberculosis had been made, with a dysphagia supposed to be adenopathic compression, esophagoscopy examination revealed an extension of malignant disease primary in the lung; in 1 case a glandular-celled carcinoma, in the other a lymphosarcoma. In both cases the pulmonary lesion was revealed by bronchoscopy. Without a diagnostic bronchoscopy neoplasms of the lung are often treated for months, even years, under a mistaken diagnosis of tuberculosis.

Multiple Primary Growths. In 2 of our cases two apparently separate lesions were found, the one about 2 or 3 cm. below the other, specimens from each showing the same type of growth, squamous-celled epithelioma. The esophageal mucosa between seemed normal. Whether or not they were instances of implantation metastases or of primary foci it is impossible to say; but there was no doubt about the isolation of the respective lesions so far as gross esophagoscopy appearances of the mucosa were concerned. The same condition may have existed in other cases, but it is only rarely that a cancerous growth is seen early enough to pass beyond it for exploration of the subjacent esophagus.

Metastases. Our records are so incomplete on the matter of metastases that it would be very misleading to give a summary. Unless the metastases were palpable in the neck, revealed in the ray or at the relatively few autopsies, no note was made.

Ulceration was present in most of the late cases of endoesophageal growths. It was more often apparent at peroral esophagoscopy than at retrograde esophagoscopy. It would seem, therefore, that the upper margin of the growth ulcerates earlier than the lower margin. In some cases the ulceration seemed to be an extensive melting away of the tissues with deep, sloughing, very foul areas. Some of these cases had a lumen larger than normal and had no dysphagia.

Location of the lesions in reference to the region is referred to under etiology. The location as to endoesophageal or periesophageal growths could not be determined positively in many of the cases because of the lateness of the stage of the disease at which the patient came in. The histologically evident types of structure, given in a foregoing paragraph, justify the inference that most of the esophageal growths start in the esophageal wall, and chiefly in the mucosa.

Symptomatology. *Early Symptoms.* It would be better for suffering humanity if all mention of symptoms were omitted with the exception of those listed below as "early symptoms." Practically all other symptoms are so late that to enumerate them serves only to perpetuate the fatal fault of late diagnosis on which the present 100 per cent mortality of this disease depends. These symptoms may seem trifling and vague—and they *are* trifling and vague—so much so that the patient often fails to notice them or is ashamed to mention them, and the practitioner either ignores them or attributes them to hysteria or morbid introspection. Often the patient is given a tonic at the only stage in which there will ever be any hope of curing the disease. These most important early symptoms are not mentioned in the textbooks or journal articles. They are described by the patient in such vague and varying terms that it is difficult to formulate them; but we shall give them as nearly as possible in the patient's own words. In most instances these symptoms had not been connected by the patient directly with the later trouble and were recalled only after close questioning:

1. "Slight, queer feeling in swallowing; but food went down all right."
2. "A feeling of nervousness about starting to swallow; after starting, food went down without any trouble."
3. "A feeling of nervousness in the neck."
4. "Vague sensation about the neck as of something wrong."
5. "A feeling of cramp around the neck."
6. "A feeling as if my swallow was not working right, but nothing seemed to stick until here lately."
7. Food "sticking in the throat while eating in a hurry; but it went down itself all right, and I had no trouble for months afterward; though I did not eat in a hurry any more."

8. "A feeling as of a lump rising in my throat." This occurred in many cases. In some patients it had no relation to eating; in other patients it occurred at sight of food or thoughts of eating; in other patients at the beginning of a meal, but disappearing after a few mouthfuls had been swallowed.

The foregoing early symptoms were elicited by close questioning of the patients as to the onset of the disease. The patients were not sent in during this initial stage because neither they nor their physicians realized the importance of the symptoms. Many patients have stated that their physicians had said the trouble was "just nervousness." Evidently it was considered a "globus hystericus." This condition we know, even when occurring as a manifestation of hysteria, to be not imaginary, but a spasmodic contraction of certain cervical or pharyngeal muscles, usually including the cricopharyngeus;⁶ and such it seems to be in cases of foreign body and of organic disease of the esophagus, such as malignancy. When the spasm is excited by a malignant lesion this lesion is quite as often in the lower two-thirds of the esophagus as close to the cricopharyngeus muscle. In the cases in which the just mentioned vague statements were made by the patients the cancer was in most instances in the thoracic esophagus. This is not remarkable when we recall the insensitiveness of the thoracic esophagus and indefiniteness of localization of subjective sensations in this region. For instance, pain from a lesion in the thoracic esophagus may be referred to the back, the epigastrium, the neck, the shoulder, or even to some more remote location.

Cough is sometimes an early symptom. Most cases of unexplained cough should be esophagoscoped as well as bronchoscoped.

Late Symptoms. It would be better for the development of thoracic surgery, and for the ultimate good of humanity, if the late symptoms were not mentioned at all. It is necessary, however, to include them here in order to present the palliative methods that have been found to prolong life and lessen suffering in the cases that have come to the Bronchoscopic Clinic.

Dysphagia, odynphagia, pain, weight loss, hematemesis, emaciation and cachexia are all hopelessly late, so far as any attempt at cure of malignancy is concerned. When encountered, however, they call loudly for immediate ray study and esophagoscopy to discover and cure benign conditions, and to establish early the palliative measures that will prolong life in hopelessly incurable, advanced cancer of the esophagus. Dysphagia, when fully developed and prominently complained of by the patient, means obstruction; and obstruction in a loose bag like the thoracic esophagus means a well advanced lesion. Food will pass a small growth. Dysphagia is noticed somewhat earlier in cancers at the cricopharyngeal and hiatal levels, but it is always a late symptom. One of the erroneous statements often made is that the dysphagia in

cancer of the esophagus is progressive. In reality, as clearly shown by our records, it is, in its early stages, much more often intermittent; so much so that one of the commonest errors in inferential diagnosis is to exclude cancer because of sudden, recent onset. Many times we have removed a bolus of food in what was supposed to be a foreign body case and found a well developed cancerous narrowing of lumen. The bolus of food had stuck either because excessively large, too hastily gulped, or too ill masticated to go through the lumen, which was adequate for better masticated food. Afterward static esophagitis and engorgement from irritation of the growth may perpetuate this suddenly appearing dysphagia. Often the artificial dentures or lack of teeth, incidental to the cancer age and conducive to ill-mastication, are blamed wholly for the stoppage; when in reality they are only partly responsible, and might even be regarded as a blessing in disguise, as giving to the alert practitioner an early sign of cancer of the esophagus. Only too often this early sign is ignored, sometimes even fatality results from an ill advised blind attempt to push the bolus downward with a bougie. Very frequently in cancer cases we get a history of such stoppage of a bolus which, however, had gone through spontaneously, resulting in an erroneous diagnosis of spasmodic stenosis by practitioners who did not realize that the day of inferential diagnosis of esophageal disease is past.

It is well to remember that dysphagia, odynphagia and spontaneous pain may be absent. In 22 of our cases the esophageal cancer had not produced any difficulty in swallowing. The lesion was discovered in the cervical esophagus in 16 cases referred for study as to the cause of a cervical adenopathy. In these cases the growth was small, but the metastatic leakage had been much earlier than is usual in the lower two-thirds of the esophagus. In the other 6 cases the absence of dysphagia was evidently due to the sloughing, liquefying nature of the growth. In these cases esophagoscopy was done in a search for the cause of melena.

Odynphagia and spontaneous pain are also very late symptoms, pain being later, perhaps, than in cancer in any other region of the body. There is, often, distress from irritation of stagnant food and coexistent esophagitis; but the typical cancer pain associated with cancer elsewhere usually comes very late. In many cases the pain is never so severe as that seen in peptic ulcer of the esophagus. Often the pain of cancer is less than that of esophagitis.

Hoarseness is nearly always present, in some degree, late in the progress of the case. Sometimes it is due to recurrent paralysis, as mentioned in the textbooks; but much more frequently it is due to an overlooked factor, namely, the overflow into the larynx of secretions and even of food and drink, owing to the subjacent esophageal obstruction. This most common cause of hoarseness has been overlooked in the literature. Occasionally it is due to

arytenoid fixation from direct extension into the laryngeal motor mechanism from postcricoid cancer. When paralysis is present it is much more frequently unilateral than bilateral. Obviously paralysis can result only from growths or metastases high enough to involve the recurrent nerve fibers, roughly speaking, in the upper half of the esophagus.

Cough may be a late symptom from overflow of secretions into the larynx, because of absent or defective esophageal drainage of normal secretions. This mechanism is often overlooked. In some cases a severe laryngotracheobronchitis may result. Cough may also be present as a reflex from the neighborhood of the growth. Cough, productive of secretions, blood or food, may be present from erosion of the growth through the wall of the trachea or a bronchus, oftener the left, or, occasionally, into the parenchyma of the lung, oftener the right.

Diagnosis. There are only two means by which an early diagnosis of cancer of the esophagus can be made, namely:

1. Roentgen-ray examination.
2. Esophagoscopy.

Only by these means will the diagnosis ever be made early enough to give the surgeon a chance to develop the technic of a curative operation; only by these means can efficient palliation be started in time to prolong the patient's life. All other means are *always negative in the early stages*.

Roentgen-ray Examination. All esophagoscopists will agree with Ellen J. Patterson⁸ that roentgen-ray examination should always precede the esophagoscopy. In most cases the roentgenologist's diagnosis will be correct; for absolute certainty esophagoscopy should follow the roentgen-ray examination. The fluoroscopic examination will reveal the esophagus in action; in other words, it permits examination of the *function* of the esophagus—something that cannot be got in any other way, not even with the esophagoscope. The fluoroscopic examination will not only often reveal evidence of malignancy, but it will exclude aneurysm. This condition is not a contraindication to esophagoscopy, because no esophagoscopist would poke his tube into an aneurysm involving the esophagus, which, of course, he can plainly see ahead of his tube-mouth; but when the fluoroscopist reports a sacculated aneurysm against which the opaque mixture stops, or past which it slowly trickles, the diagnosis has been made and the indications for treatment are plain.

Ray films, especially a well made stereoscopic pair, interpreted by an experienced roentgenologist, afford a very reliable means of diagnosis, and, taken with the fluoroscopic findings, the ray diagnosis will rarely call for revision. One invaluable diagnostic point afforded by the ray is information as to the lateral extent of the growth.

This information can be had in no other way. As to the technical consideration of roentgen-ray diagnosis the reader is referred to to the articles by Manges,⁹ Pancoast,¹⁰ Pfahler,¹¹ Bowen,¹² Hirsch¹³ and many other scientific and skilful roentgenologists who have studied this problem and developed the technic to its present point of practical perfection.

It is necessary here to emphasize the necessity of attaching no importance whatever to negative ray findings except those of experts with the best apparatus. Many hospitals are handicapped in being unable to afford the best and latest of the frequently improved apparatus. Under these circumstances it is especially necessary to beware of negative findings. Even under these circumstances, if they cannot be bettered, it is in all cases necessary to resort to the ray examination as the first step in the diagnosis.

Esophagoscopy. This is the final arbiter which gives all the certainty of direct examination with the eye, yielding objective evidence that, taken with the roentgen-ray examination, which is also an objective method, relegates all inferential methods to third place, if not to desuetude. All inferential methods, including the bougie, depend upon obstruction, whereas with the esophagoscope the walls of the esophagus are examined for the presence of lesions. Every crease and fold is exposed to inspection by the eye. The great safeguard in esophagoscopy as compared with the bougie and all similar methods is that you can see what is ahead of the distal end. You do not push when you see tissue, normal or abnormal, ahead of the tube-mouth. By the esophagoscopic appearances alone the diagnosis has been correct in about 92 per cent of the cases of endoesophageal cancer at the Bronchoscopic Clinic, inconclusive in 6 per cent, unconfirmed in 2 per cent. These figures omit consideration of biopsy; in no instance has a positive histologic diagnosis of cancer been proven erroneous.

With the esophagoscope we have been able to make a diagnosis before the stenotic stage in 28 patients, and we have every reason to believe we could have made it thus early in practically all the cases of esophageal disease that started endoesophageally if they had reached the esophagoscopist early.

If for any reason a first esophagoscopy is inconclusive, a second esophagoscopy or as many more as desired may be done. Being done without anesthesia, general or local, and, if the patient is in good condition, without hospitalization, it has sometimes been deemed advisable to study a case at esophagoscopies repeated every week or oftener. Prolonged fasting is unnecessary; four hours are deemed sufficient after liquid food. In a few weeks esophagoscopic and roentgenologic study has usually sufficed to clear away all doubt even in the most obscure cases of periesophageal malignancy.

DESCRIPTION OF PLATE I.

ILLUSTRATION OF THE MISLEADING AND FATAL RESULTS OF BLIND BOUGINAGE FOR DIAGNOSIS. PAINTED FROM A POSTMORTEM SPECIMEN BY THE AUTHOR.

The patient had been admitted moribund with mediastinal hemorrhage and emphysema. The trachea is opened through the "rings" to the right of the membranous posterior wall; the larynx is laid open from behind; the esophagus is split down the right wall as far as the diaphragm. The perforation evidently had been made by a bougie, shortly before admission, causing the fatal mediastinal hemorrhage shown by the huge blood-clot. The edges of the perforation showed no histologic evidence of malignancy. The bougie had evidently gone through normal esophageal wall, where the lumen was not pathologically stenosed, above the cricopharyngeus, and far above the cancer, which is seen in the esophagus at the level of the diaphragm surrounded by a mass of lymph nodes under the pleura. The danger of perforation by a blindly passed bougie through cancerous tissue is frequently mentioned, but the greater danger of perforation of the perfectly normal wall is not so generally realized. It is also noteworthy that this patient was treated for a supposed "cardiospasm" at three different clinics before reaching the place where an erroneous diagnosis of cancer of the cervical esophagus was made because the bougie was arrested in the neck and came back bloody! No esophagoscopy was done in this case because the patient was dying when admitted.

PLATE II.

ENDOSCOPIC VIEWS OF CARCINOMA AND SARCOMA OF THE ESOPHAGUS.

These views were sketched by the author from memory shortly after the respective esophagoscopies, hence represent a view of the interior of the esophagus at a certain level in the particular cases, the patient being in the dorsal position in each instance. No anesthetic, general or local, was used, a fact which must be borne in mind when considering color. The sketches serve to illustrate the modern method of diagnosis of esophageal disease by looking at the lesion. They also show how accurately a specimen, when desirable, can be taken from any selected part of the lesion.

1. Normal esophageal folds as seen at the moment the esophagoscope enters the thoracic esophagus. The delicate pink, velvety surfaces, the soft folds flattening without resistance at the approach of the tube-mouth and yielding to the slightest manipulation of the tubal lip; the resilient respiratory recession and advance; the pulsatory movement of one wall at certain levels;—all these are, esophagoscopically, so characteristic of the normal esophagus, to the accustomed observer, that any abnormality in color, form or movement is instantly apparent. The sketch shows the image during the momentary pause at the end of the expiratory phase.

2. Whitish, nodular form of carcinoma on the posterior wall of the upper end of the esophagus in a woman, aged fifty-eight years, who for over a year and a half was thought to have had "spasm of the esophageal muscles." "cardiospasm," "neurasthenia," "major hysteria," finally "mental derangement," because of increasing "globus hystericus" and, later, "refusal" (!) to swallow food, for which she was ultimately placed in a psychopathic institution. She was fed with a stomach-tube, the passage of which was thought to rule out organic esophageal disease. After having consulted specialists in various parts of the world she came under the observation of an internist who at once decided the esophagus should be looked at with the esophagoscope. It required thirty seconds to find the lesion, make an esophagoscopic diagnosis of cancer and take a specimen, which Dr. B. L. Crawford found to be a squamous-celled epithelioma. The symptomatic simulation of a neurosis by cancer of the esophagus is very frequently observed by esophagoscopists.

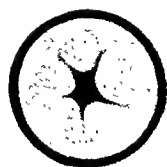
3. Cancer of the thoracic esophagus in a man, aged twenty-six years, sent in with a diagnosis of "cardiospasm." Form more often than color is the esophagoscopic criterion of malignancy. The anterior (upper) fold is not very different in color from the normal mucosa, but it is granular, almost nodular, with fungations which at a later stage are often quite exuberant. The creases between the folds are filled with oozing blood.

4. Cancerous infiltration of the thoracic esophageal wall in a man, aged forty-five years, supposed to have spasmodic stenosis in the middle-third of the esophagus. Here again the color of the mucosa was not far from normal; but the hardness, the rigidity, the absence of the normal characteristics of movement incidental to respiration, pulsation and manipulation described above (1) were deemed so characteristic of malignant infiltration that an esophagoscopic diagnosis of cancer was made. As it was deemed inadvisable to take a specimen at this stage, it was

PLATE I



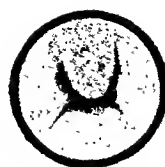
PLATE II



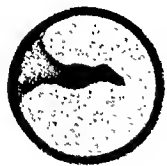
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Chevaller Jackson, 1924

requested that the patient be sent back in six weeks. (See the legend to the following illustration, 5.) An esophagoscopy diagnosis of malignancy was made, however, on the conditions here described, and an immediate gastrostomy was advised, but was postponed.

5. Same patient as in the preceding illustration (4). The anterior rounded ridge of infiltration has ulcerated; a center slough, discolored with bismuth sulphide, is ready to come away. The edges are beginning to fungate, which renders the taking of a specimen perfectly safe. This was done, and Dr. B. L. Crawford reported upon the specimen, squamous-celled epithelioma. The relatively rapid progress of the ulceration was probably due to the constant presence of stagnant, fermenting, irritating food.

6. On the right wall is seen an old scar. This was probably due to the swallowing of lye, twenty years before, of which there was a very clear history. The bleeding fungations at the distal edge of the scar looked so suspicious of malignancy that they were nipped off and sent to the laboratory. Dr. Ernest W. Willetts reported upon the specimen as undoubtedly squamous-celled epithelioma.

7. Boy, aged sixteen years. Lymphosarcoma involving the anterior wall of the esophagus, at the level of the crossing of the left bronchus. This patient had no difficulty in swallowing. He was supposed to have asthma, causing him to "wheeze and to cough until he vomited." He was referred for bronchoscopy because of the asthmatic symptoms. The bronchoscopic findings shown in the following illustration (8) led to the esophagoscopy. Air-bubbles were seen at the depressed necrotic area, and a hissing sound was heard through the esophagoscope when the patient voluntarily coughed at request. Part at least of the dark grayish color of the exudate is due to sulphided bismuth.

8. View down the left main bronchus of the patient referred to in the preceding illustration (7). The bleeding granular mass on the posterior wall of the bronchus evidently was part of the growth visible esophagoscopically (7). What appears like a grayish slough was partially sulphided, swallowed bismuth that came through from the esophagus. Blood was oozing among the fungations.

9. Woman, aged forty-two years. Difficulty in swallowing diagnosticated cancerous on three previous occasions because of arrest of the bougie, the tip of which came back bloody, and of the history of progressive dysphagia and emaciation. The yellow, globular mass protruding in the ragged, irregular opening was scooped out with the mechanical spoon and found to be cheesy debris and thick pus, with a few giant cells and elements of glandular structure. No tubercle bacilli were found, but Dr. Ernest W. Willetts deemed the process suppurating tuberculosis of the mediastinal glands rupturing into the esophagus. There was no clinical or ray evidence of active pulmonary tuberculosis. Dr. Russell H. Boggs stated that there were slight indications of healed apical lesions. The patient made a good recovery, with normal swallowing, and was above normal weight four years later.

10. Man, aged forty-seven years. Gastrostomy had been done before admission. This illustration shows a mixed lesion, luetic and cancerous. The large, smooth, rounded mass on the left wall was not very hard and was movable with the tube-mouth. Because of the 4 + Wassermann reaction it was deemed best not to take a specimen. The patient was put upon energetic antiluetic treatment, which resulted in the total disappearance of the dysphagia.

11. The same patient as in the preceding illustration (10); esophagoscopy appearances after two months of energetic antiluetic treatment (KI and Hg prot.). The nodular mass, which was probably a gumma, is seen to have disappeared; but the granular mass has increased in extent and is fungating exuberantly and oozing blood freely. Three endoscopists at the Bronchoscopic Clinic were unanimously of the opinion that the fungating lesion was cancerous. This diagnosis was doubted by the attending physician because of the total disappearance of dysphagia under antiluetic treatment, the gastrostomy tube having been entirely abandoned. A specimen was therefore taken and was reported by Dr. Baxter L. Crawford as squamous-celled epithelioma. The progress of this case confirmed this diagnosis.

12. Peptic ulcer of the esophagus in a man, aged forty-seven years, suffering from dysphagia, odynphagia, severe nocturnal substernal pain extending through to the back. These symptoms, with obstruction to the passage of a bougie which came back bloody had led to the diagnosis of cancer of the esophagus. The patient was emaciated apparently from pain, sleepless nights and worry in anticipation of a death by cancer, rather than from lack of nourishment. The border of the ulcer was not hard and a small esophagoscope would pass it, going on through the hiatal esophagus into the stomach, which was about eight centimeters below the lower border of the lesion. A specimen removed from the edge of the ulcer showed no evidence of malignancy; only inflammation and ulceration. Histologic elements of gastric mucosa and glandular structure led to the diagnosis of peptic ulcer of the esophagus, starting in an esophageal island of gastric mucosa.

To get a chance to make an early diagnosis of cancer of the esophagus, it is necessary to see patients before the development of more than a very slight degree of stenosis. As noted under symptomatology, very vague descriptions by the patient of early symptoms are often either overlooked or classed as "globus hystericus." It is to be expected that if every patient complaining of the vague symptoms referred to under symptomatology is esophagoscoped, many purely neurotic patients will be examined. But this is incapable if cancer of the esophagus is to be diagnosticated early. Over and over again we have made an inferential diagnosis of globus hystericus, or of a neurotic condition, passed an esophagoscope and found a cancer of the esophagus. There is no way in which to distinguish between the globus of hysteria and the globus of organic disease except by the esophagoscope. As elsewhere herein mentioned, the opinion of the roentgenologist is often decisive as to purely neurotic conditions, and should always be had before esophagoscopy; but usually the roentgenologist will advise esophagoscopy also. In no case is full justice done to the patient in making an inferential diagnosis of globus hystericus without the ocular evidence afforded by the roentgen-ray and the esophagoscope.

Esophagoscopic Appearances. Endoesophageal malignancy develops at a very early stage characteristic and unmistakable appearances. These have been fully described (Jackson⁶), and are well known to esophagoscopists. Anyone who has seen many cases of cancer in the pharynx and who is also accustomed to monocular vision through an endoscopic tube, will rarely, if ever, fail to recognize ulcerative, fungating cancer of the esophagus, such as illustrated in Plate II. Some delay in esophagoscopic diagnosis arises in the periesophageal growths producing a compression stenosis of the esophageal lumen. In these cases the presence of a hard, stenosing mass palpable with the tube-mouth outside the wall and obliterating the soft, resilient unfolding of the normal esophageal wall (1, Plate II) is diagnostic to the experienced esophagoscopist. When these appearances are present the esophagoscopist will always consult with the roentgenologist who is able in practically every such case to outline the exterior border of a periesophageal growth. The internist will exclude pulmonary tuberculous and suppurative disease that might produce a secondary compressive adenitis, and lues will be excluded by the usual means.

Approached thus from four angles the diagnosis of periesophageal malignancy comes as near certainty as is possible in any neoplastic disease without biopsy. Certainly, the percentage of error will be small even if we were compelled to stop there. But in a large percentage of cases of periesophageal disease a subsequent esophagoscopy after a month or two will show the fungating form of lesion from which a specimen may safely be taken. Anyway, it is not in the periesophageal, but in the much more frequent endo-

esophageal cancers that hope of surgical cure lies. In considering esophagoscopic appearances it must be remembered that mediastinal abscess may compress the esophagus; but it is softer to palpation with the tube-mouth or swab. At a later stage, when the abscess has discharged into the esophagus, the orifice of the fistula may be confusing, especially if granulations are exuberant; but the oozing of pus is usually quite noticeable; and, most important, in all such cases it is at once manifest to the esophagoscopist that a specimen may be taken with perfect safety. The histologic report will be decisive. If the first specimen be inconclusive, a second, or as many as desired, may be taken at subsequent esophagoscopies.

Peptic Ulcer. There is only one condition with which cancer is likely to be confused in esophagoscopic appearances, namely, that rare condition, peptic ulcer. Minor mucosal erosions of the esophagus are relatively common, and aphthous ulcers are not very rare; but large, deep ulcerations are so rare that many esophagoscopists of large experience have not seen a case. In all there have been 16 of these cases that have come to the Bronchoscopic Clinic. All but 2 of them were in the lower third of the esophagus, and in 6 of them histologic structure suggestive of gastric mucosa was demonstrable. That all of them were located on islands of gastric mucosa is possible, but there was nothing to substantiate such a belief in any except the 6 cases. The esophagoscopic appearance of these peptic ulcers as elsewhere described by the author is not unlike the gastroscopic appearances of gastric ulcer. In all cases of suspected peptic ulcer of the esophagus, biopsy will decide with certainty.

Biopsy. In over 92 per cent of the cases the diagnosis by esophagoscopic appearances alone ultimately has been found correct. So far as a palliative treatment such as gastrostomy is concerned, no specimen need be taken, because such measures are strongly indicated anyway; but when it comes to a radical surgical procedure, such as transthoracic esophagotomy, the surgeon desires to have peptic ulcer, gumma, foreign body, esophagitis, cicatricial and spasmodic stenosis and other benign conditions excluded before undertaking a possibly fatal exploration. Histologic examination of an esophagoscopically removed specimen affords the absolute certainty that is necessary to get a man in good general health to submit to an operation of very high mortality. If the patient is not in good condition he will not survive the operation. During our more than thirty years' experience we have never had a histologic diagnosis of cancer based upon an esophagoscopically removed specimen found absolutely erroneous. Specimens sometimes are inconclusive, but when this occurs other specimens are taken. There are often cases in which we deem it unnecessary to take a specimen, and there are other cases in which we deem it unwise to take one. In the latter case a later esophagoscopy will usually reveal a lesion

from which a specimen may be taken with safety. No anesthetic, general or local, is used. Esophageal lesions, neoplastic or otherwise, are insensitive to the taking of a specimen of tissue.

Examination of the Patient. As just stated, esophagoscopy is the one great and only method without which a diagnosis of esophageal cancer cannot be made early and without which a diagnosis cannot be made with certainty, even late. It follows, therefore, that esophagoscopy should be done in every patient presenting any symptom whatever of the slightest abnormality in the swallowing function.

However, this does not mean that esophagoscopy is the first step in the making of a diagnosis. On the contrary, while it is first in importance, it is the last step in the orderly procedure by which a diagnosis of esophageal disease should be made.

The following are the steps in the procedure for the diagnosis of esophageal disease at the Bronchoscopic Clinic:

1. A complete history is taken.
2. Complete examination of nose and throat, including mirror examination as to: (a) Defective motility of the larynx, (b) infiltration from extension of a hypopharyngeal growth, and (c) accumulations of secretions in the pyriform fossæ, indicating impaired esophageal drainage. Any or all of these may indicate esophageal disease. Severe dysphagia and odynphagia may be due to disease, benign or malignant, of the epiglottis, pharynx or larynx.
3. Physical examination, complete, including careful examination of the lungs, heart, circulation, etc.
4. Urinalysis, sputum test, hemoglobin test, blood count, etc.
5. Wassermann test.
6. Fluoroscopic examination first for aneurysm, then with an opaque mixture, as to the functioning of the esophagus.
7. Roentgen-ray examination of the chest for disease of the pleura, lungs, heart and mediastinum as well as the esophagus; first without then with a swallowed opaque mixture.
8. Complete gastrointestinal ray study. This sometimes is omitted, but omission is seldom advisable unless a hopelessly advanced cancer of the esophagus is discovered by the previous ray study.

Positive findings in any of the foregoing examinations do not necessarily obviate the necessity for an esophagoscopy, nor contraindicate it. But extensive, painful, ulcerative tuberculosis of the epiglottis or larynx, for instance, with a fluoroscopically normal esophageal lumen and swallowing function, constitute a combination of evidence upon which we often decide not to do an esophagoscopy or to postpone it pending further observation. If, however, fluoroscopy shows narrowing of the mediastinal esophageal lumen, as by glands or neoplasm, esophagoscopy may be called for in cases with tuberculous laryngeal disease. In malignant disease of the larynx, unlike tuberculous laryngeal disease, esophagoscopy

is of the utmost importance to determine contraindicating metastases along the hypopharyngeal or esophageal wall. If there are nodular elevations or compression or infiltration of the wall of the thoracic esophagus indicating mediastinal metastases, laryngectomy is hopeless and contraindicated (Jackson⁶).

A patient with lues or pulmonary tuberculosis may have cancer of the esophagus. We have seen quite a number of such coincident diseases, though rarely as mixed lesions, as elsewhere herein mentioned. We often decide, in case of a strongly plus Wassermann test, to wait for a thorough course of mercury before doing esophagoscopy for diagnosis.

Errors in Diagnosis. Practically all the errors in diagnosis of esophageal malignancy arise from dependence on methods that are always negative in the early stages and on inference instead of objective evidence. Of 110 cases of esophagoscopically proven malignant disease of the esophagus, in 87 an inferential diagnosis of neurotic conditions had previously been made either by ourselves, tentatively, or by our predecessors tentatively or positively.

One of the most common errors in the inferential diagnosis of esophageal disease based on the history of the case is to exclude cancer in favor of spasm because of the patient's positive assertion that he never had any trouble in swallowing until a few days or weeks previously, when suddenly a piece of meat or other food stuck because insufficiently masticated. This sudden onset of symptoms is very common in cancer (Turner¹). In many such cases at the Bronchoscopic Clinic we have found well-developed cancer which must have been present for many months. Any well-masticated food will, without difficulty, go through an esophageal lumen of 6 mm. diameter; yet an imperfectly masticated bolus will stick, for a time, at least. It is not until this happens that the patient's attention is called to any difficulty in swallowing. This explains the sudden onset. In other instances a sloughing type of growth may be at times only slightly obstructive. But why do the patient injustice of trying to make an inferential diagnosis of esophageal disease when the esophagus is open to direct examination of the eye by a simple and safe technic that requires no anesthetic, general or local, and no hospitalization; that involves no more annoyance than having a tooth filled; and that requires but a few minutes?

Apart from the vague "neurotic" symptoms elsewhere herein referred to, there is only one point in the history of the case that is of great importance in the early diagnosis of cancer of the esophagus, and that is the history of food having at some time or other stuck for a moment or longer. But this is not diagnostic. In other words the history of the case is of value chiefly as eliciting an indication for esophagoscopy. It cannot be too strongly urged that it should be part of all routine history taking in all hospitals

to ask every patient, regardless of the chief complaint, these two questions:

"1. Have you ever noticed any trouble in swallowing food or liquids?"

"2. Do you remember ever having had food lodge for a time before going down?"

All internes should be thus instructed and all printed instructions for the filling in of history blanks should have these questions printed on them. By this means opportunities for early esophagoscopic diagnosis would be afforded and many diagnostic errors would be eliminated.

In 12 cases of cancer of the esophagus coming to the clinic the patients had an enlarged and diseased lingual tonsil, and in 4 of the cases we felt inclined inferentially to regard this as the cause of the dysphagia of which the patients complained. In all 12 cases, however, esophagoscopy revealed a cancer in the esophagus. In a number of other cases, however, esophagoscopy showed the esophagus to be normal. Therefore while the lingual tonsil should always be thought of as a cause of dysphagia, as so well demonstrated by J. Arnold Jones,¹⁴ every such case should be esophagoscoped. Endocrine disturbance, as suggested by Mr. Jones, may be very intimately connected with globus hystericus and the vague sensations often noted in such cases; but malignant disease of the esophagus occasionally at its very incipency gives rise to sensations quite as vaguely described by the patient. If we are ever going to diagnosticate esophageal and hypopharyngeal malignancy early, almost all of these patients must be esophagoscoped.

One of the most frequent of diagnostic errors arises from the use of the blind bougie, which is in reality an inferential method. Those who use it infer that when it goes through there is no cancer, though it may have gone through the esophageal wall into the mediastinum, or have passed a small early or late sloughing nonobstructive cancer; if it meet an obstruction they infer that the obstruction is cancerous, even though the obstruction may be normal wall; if it show blood on withdrawal, they infer that the blood comes from a cancer and not from normal or inflamed mucosa; if it be foul they infer that the odor comes from an ulcerating cancer and not from stagnant food and secretions, or a septic mouth, or septic faucial lymphoid tissue. There have come to the Bronchoscopic Clinic 21 cases of cancer of the *lower* end of the esophagus in which an erroneous diagnosis of cancer of the *upper* end of the esophagus had been previously made by the bougie. These erroneous diagnoses were all made with localization at about 15 to 17 cm. from the upper teeth, which is the level of the cricopharyngeal fold. This region was found normal at esophagoscopy except in the cases in which a false passage was found.

All esophagoscopists agree with the following admirable sum-

mary of Mr. Tilley,¹⁵ giving reasons why a bougie should never be used in a case of suspected cancer:

"1. It may fail to detect any obstruction when the growth is small, or even in advanced cases when rapid ulceration fails to produce stenosis.

"2. If an obstruction is met with, the bougie affords no more than presumptive evidence of its nature.

"3. Fatal results have followed the use of the bougie even in skilled hands, as a result of perforation of the thin diseased walls of the esophagus in the immediate neighborhood of the growth."

To this I should like to add a supplementary paragraph:

4. Fatal results have followed the use of the bougie as a result of perforation of the perfectly normal wall of the esophagus far above the growth in some cases, and in other cases in which no growth whatever existed.

Plate I illustrates a case of death from mediastinal hemorrhage due to blind bouginage in skillful hands. Arrowsmith¹⁶ and many others have reported similar cases in the literature. Similar cases are shown by specimens in many large medical and surgical museums in this country and Europe. Trousseau said, in effect, that all these patients died sooner or later of the bougie.

If for any reason an esophagoscopist were unavailable we would abide by the decision of a competent roentgenologist, and under no circumstances would we submit our patient to the risk of the dangerous, inconclusive bougie.

Prognosis. It was stated by the author,⁶ many years ago, that the mortality of malignant disease of the esophagus was, at that time, 100 per cent. Notwithstanding the great advances since made in the surgery of malignancy elsewhere in the body the ultimate prognosis of esophageal cancer remains the same today. There is every reason to believe, however, that the reason for this is that the surgeons have never had a chance to develop the technic of a curative operation because the diagnosis is never made early. The reason why the diagnosis is never made early is that the textbooks and journal articles give chiefly or exclusively diagnostic methods that *are always negative early* in the disease. When the time comes in which esophagoscopy shall be resorted to promptly on the appearance of certain very vague symptoms there is ample justification for the belief that the surgeon will cure a good percentage of patients. Squamous-celled endoesophageal carcinoma is not an aggressive type of malignancy. On the contrary it is a mild, slow and for a long time purely local process. Under palliative treatment, if the patient is never permitted to be short of an abundance of water and a full allowance of properly balanced food elements, most cases will survive at least two years from the onset of the disease, and some have survived as long as five years. One lived six years. Patients running the gauntlet of late inferen-

tial diagnosis, and leading a precarious existence of various degrees of food and water starvation, depressed and acidotic, on a diet of intermittent supplies of raw eggs and meat broths, may not survive a year from the probable time of the onset of the disease.

Treatment. *Resection of the Esophagus.* Until some now unknown method of treatment of cancer of the esophagus shall have been discovered we must look to the surgeon for hope of cure. Nor should the gravity of the procedure deter us, since we know that the disease involves 100 per cent mortality. There is good reason to believe endoesophageal cancer is curable surgically, at some levels at least, if a sufficiently early diagnosis be made. The fundamental reason for the thousands of agonizing deaths from cancer of the esophagus is false education. The mind of the medical student and the medical profession is so saturated with the idea that cancer of the esophagus is to be detected by obstruction to the passage of a bougie, in a patient with dysphagia, pain, cachexia and emaciation, that the surgeon never gets a chance to cure esophageal cancer while it is still a local process. When every patient mentioning the slightest abnormality in swallowing, or even slightest abnormal sensation in the cervical, retrosternal or epigastric region, is considered not necessarily neurotic, but possibly cancerous, surgery will show better results. When such a patient shall be referred at once to the roentgenologist for fluoroscopic and roentgenographic study of the esophagus, esophageal cancer will be discovered early and a new era in esophageal surgery will have been established. In most of such cases esophagoscopy should follow the roentgen-ray examination, and always in all cases in which the roentgenologist suspects esophageal abnormality. Few surgeons today would wish to expose transthoracically the mediastinal esophagus with a view to resection for cancer without having the esophagoscopist's confirmation of the diagnosis. When a diagnosis can be made by other means it is not only uncertain, but the patient almost invariably has become a bad subject for a major operation. Practically all esophageal resections up to the present time are done upon such cases. It is no wonder the results are so discouraging. They would be so with cancer anywhere in the body.

The foregoing statement of opinion as to the surgical curability of early esophageal cancer is based not on cures, but on some of the findings at the Bronchoscopic Clinic, which may be summarized as follows:

1. Over 90 per cent of all the cases fall into two classes, namely:
 - (a) Adenocarcinomata at the lower end of the esophagus.
 - (b) Squamous-celled cancer in other locations.
2. This leads to the conclusion that the disease at the lower end of the esophagus started at the cardiac margin. If discovered at the start, such cases would offer good chances of cure by excision through an abdominal incision. We do not refer here to extensive gastric cancer reaching the esophagus very late.

3. The squamous-celled type, which with us has been the most common, means in most cases an endoesophageal beginning. Here we have a local process of a relatively low degree of malignancy. It is reasonable to expect a good percentage of cures if the surgeon could get the patient in this stage, but he never does, and never will, so long as present obsolete diagnostic methods are taught in the medical schools and promulgated in our journals and text-books. Our experience abundantly confirms the statement of Willy Meyer¹⁷ when he says:

"There is one important characteristic of cancer of the esophagus that should be especially emphasized, namely, that it is the most benign of all carcinomas of the gastrointestinal tract. Its growth is comparatively slow; it remains localized for a long time; has little tendency to metastasis in other parts of the body, or in the lymphatic glands, and is not very apt to recur."

Splendid fundamental work in resection of the esophagus has been done by Torek,¹⁸ Miller,¹⁹ Meyer,¹⁷ Janeway and Green,²⁰ Lilienthal,²¹ Muller,²² Hedblom²³ and others. The lacking essential is early diagnosis, which could be furnished by esophagoscopy not only early, but with the absolute certainty essential to getting the consent of a comparatively well man to an operation he may not survive.

Palliative Treatment. The most important palliative measure is very early gastrostomy to stop the mechanical irritation of passing and lodging food and the chemical irritation of fermenting and stagnant food and secretions saturated with oral infections. As Da Costa and Shallow have said, "No surgeon would stretch a cancer." Instead of trying temporary mechanical means to keep the esophagus open, it is better to follow the cardinal rule of surgery to "Let the inoperable cancerous mass alone; put it at rest." The writers who oppose gastrostomy state that it has had, in their hands, a very high operative mortality. These two facts must be taken together. Opposition to gastrostomy means an invariably late operation. Late operations for anything always have a high mortality, but in esophageal cancer late gastrostomy means operation upon a patient moribund from cachexia, inanition, acidosis, and, worst of all, water starvation. Such patients are the worst possible surgical subjects, even for a minor operation. It is no wonder they fail to react. The tissues will not take up water after it is put in the stomach in the worst cases. Up to this time the case has been a medical one. It is now turned over to the surgeon. No wonder the surgeon joins in condemning gastrostomy. Another reason for discrediting gastrostomy is the mental depression that really comes from acidosis. As previously pointed out,²⁴ gastrostomized patients unless watched will drift into a diet exclusively of raw eggs and meat broths. No one could be happy on such a diet even if swallowed normally. Saliva

is also necessary. If an early gastrostomy is done and the esophagus put at rest with only water by mouth, saliva will go through for a long time.

Radium is useful in some cases, as shown by Fielding O. Lewis,²⁵ Pancoast, Newcomet, Douglas Quick and others. As pointed out by Quick, overdosage must be carefully avoided.

Roentgen-ray. In our experience, in inoperable cases, patients will live longest under a combination of early gastrostomy, a varied, well balanced diet by tube, plenty of water by mouth and deep roentgen-ray treatment. We have seen objective evidence of benefit from the ray in cases treated by Manges, Pancoast Pfahler, Bowen, Cohen, Borzell and others.

Conclusions. 1. It was stated by the author many years ago that the mortality of malignant disease of the esophagus was, at that time, 100 per cent. Notwithstanding the great advances made in the surgery of malignancy elsewhere in the body the ultimate prognosis of esophageal cancer remains the same today.

2. There is every reason to believe, however, that the reason for this is that the surgeons have never had a chance to develop the technic of a curative operation because the diagnosis is never made early.

3. The reason why the diagnosis is never made early is that the textbooks and journal articles give chiefly or exclusively diagnostic methods that *are always negative early* in the disease.

4. When the time comes in which esophagoscopy shall be resorted to promptly on the appearance of certain very vague symptoms there is ample justification for the belief that the surgeon will cure a good percentage of patients.

5. Squamous-celled endoesophageal carcinoma is not an aggressive type of malignancy. On the contrary, it is a mild, slow and, for a long time, purely local process.

6. Under palliative treatment, if the patient is never permitted to be short of an abundance of water and a full allowance of properly balanced food elements, most cases will survive at least two years from the onset of the disease, and some have survived as long as five years. One lived six years.

7. Patients running the gauntlet of late inferential diagnosis, and leading a precarious existence of various degrees of food and water starvation, depressed and acidotic, on a diet of intermittent supplies of raw eggs and meat broths, may not survive more than a year from the probable time of the onset of the disease.

8. The bougie as a diagnostic means is not only dangerous, but it is inconclusive because inferential; and it is always hopelessly late. A cancer must be well advanced before it will stop a bougie. Even fatal cancer of the esophagus may not be obstructive.

9. The bougie as a therapeutic measure hastens death either by perforation or by increasing metastases. As stated by Da Costa

"No surgeon would stretch a cancer." As stated by Shallow "No surgeon would forcibly dilate malignant stricture of the esophagus any more than he would forcibly dilate cancer of the rectum."³³

10. There are only two means by which an early diagnosis of esophageal malignancy can be made, namely: (1) Roentgen-ray examination, and (2) esophagoscopy. All other means are late, inconclusive, and some of them dangerous.

11. By esophagoscopy endoesophageal cancer can be diagnosed not only early, but with the absolute certainty essential to getting the consent of a comparatively well man to an operation he may not survive.

12. Endoesophageal cancer can be diagnosed just as early, just as quickly and just as certainly as cancer of the cervix if an opportunity for esophagoscopy is afforded early.

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PULMONARY NEOPLASM: A CLINICAL STUDY OF THREE CASES.

BY DAVID GREENBERG, M.D.,

NEW YORK.

(From the Medical Service and the Pathological Laboratory of the Lebanon Hospital.)

Introduction. The accumulation of case reports both in hospital statistics and in the medical literature of new growths of the lungs is evidence of its frequency. Up to a few years ago lung neoplasm was considered to be one of the rarer medical diseases. The introduction of the roentgen-ray, however, has brought to light many cases which would otherwise have been missed. More recently the bronchoscope has come into more general use and has helped to discover neoplasm of the larger bronchi. The newer agents may enable us to turn these cases over to the surgeon or the roentgenotherapist early enough to remove them from the realm of the hopelessly incurable.

This study is based on 3 cases of lung tumor which presented totally different clinical pictures. The object of this report is to emphasize the difficulties of early diagnosis and the importance of thorough physical and laboratory investigation.

Historical. Morgagni,¹ in 1708, was probably the first to mention cancer of the lung. He mentions an autopsy where *ulcus cancrosum* was found in the lung. Bayle,² in 1810, describes 3 cases of *phthisis cancreuse*, and Laennec,³ in 1818, speaks of *encephaloid tumor* of the lung. Stokes,⁴ in 1842, describes several varieties of cancer, and Eberman,⁵ in 1857, collected 72 cases. The more important contributions to the subject, however, appeared only after cellular pathology was studied and understood. The

earliest microscopical investigations were made by Langhans,⁶ in 1871, and Marchiafava,⁷ in 1873. Subsequently many noteworthy contributions were made, and a number of original papers and reviews were published. Reinhard,⁸ in 1878, collected 27 cases; Wolf,⁹ 31 cases in 1895; Paessler,¹⁰ 74 cases in 1896; Sehrt,¹¹ 177 cases in 1904. In this country Adler¹² collected 464 cases in 1912, and Scott and Forman¹³ reported 120 additional cases in 1916. Since then, and especially following the influenza epidemic, many more cases are to be found in the literature.

Frequency. Primary malignancy of the lung is said to be present in about 1 per cent of all cancers, and about one-third of 1 per cent of all necropsies (according to Ewing¹⁴ and Adler¹²). Males are more often afflicted than females, and no age is exempt. McAldowie¹⁵ reported a case of lung tumor in an infant aged five and a half months. The greatest number of cases, however, occur between forty and seventy years of age—over 80 per cent in Adler's series. The right lung is more commonly involved than the left.

Etiology. The etiology is not known. Tuberculosis, anthracosis, chronic bronchitis, interstitial pneumonia, fibrosis, influenza and influenza-pneumonia are mentioned as possible causative factors by various authors. Manifestly no cause can be definitely established for this form of malignancy until the cause for malignancy in general is found.

Anatomy and Pathology. Both bronchi and lungs are developed from an infolding of the primitive esophagus. These consist of simple tubes lined by a double layer of epithelium, which later becomes differentiated into three distinct kinds of epithelial tissue. In the fully developed fetus the trachea and larger bronchi are lined by three layers of epithelium, an outer cylindrical-cell or goblet-cell layer, a middle layer of spindle-shaped cells and an inner layer of wedge-shaped cells resting on a basement membrane. Mucous glands are found throughout the bronchial tree being situated in the submucosa and are lined by a single layer of goblet cells. The mucous membrane of the smaller bronchi retains its ciliated columnar character, but consists of a single layer of cells gradually merging into flat pavement epithelium in the alveoli. Thus it is clear that carcinoma of the lung may arise from any of these structures, bronchial epithelium, mucous gland epithelium and alveolar epithelium.

The lymphatics of the lungs are of two kinds—deep and superficial (Miller¹⁶). The deep lymphatics are peribronchial and perivascular and anastomose at points of division of the bronchi forming plexuses. These lymphatics become sparser as the smaller bronchioles are approached, there being none in the alveolar wall. The peripheral lymphatics are distributed over the pleura, forming a fairly dense plexus and anastomose with the deep lymphatics as they follow the pleural veins. The normal flow in both these sets of lymphatics is toward the hilum.

Classification. Carcinoma of the lungs and bronchi may be classified according to gross anatomy, histology or histogenesis. Ewing's¹⁴ classification based on histogenesis is followed by most authors, three types being distinguished: (1) Tumor arising from the mucous membrane of the bronchi; (2) tumors arising from mucous gland of the bronchi; (3) tumors arising from alveolar epithelium.

To be sure, in advanced cases it is often impossible to determine from where the original tumor arose. The clinical history, together with the roentgen-ray examination, are at times of indispensable value in establishing the origin of a given tumor. Generally carcinomata of the bronchial epithelium follows along the walls of the bronchi, at times filling the lumen with papillary projections. In some cases necrosis occurs in the superficial tissue, leading to excavation and bronchiectasis. The surrounding pulmonary tissue (alveoli) becomes involved later, but not as uniformly nor as completely as in tumor arising from the pulmonary alveoli. Carcinoma arising from mucous glands sometimes produce characteristic tumors possessing many goblet cells. They are usually limited to the bronchial wall, the lining epithelium of the bronchi remaining intact and stenosis rather than dilatation of the bronchi is the rule. Microscopically these tumors may contain numerous secreting or goblet cells. Carcinoma arising from pulmonary alveoli may be diffuse or nodular, and necrosis is a prominent feature. In their growth they produce either complete or partial filling of the alveoli with cuboidal, cylindrical or flat cells. Squamous-cell tumors, however, may also arise in the bronchi. According to histological appearance, three types are described cylindrical-cell tumors, polymorphous-cell tumors and squamous-cell tumors. Some use a purely clinical classification based on whether or not the tumor in the lung is local, diffuse or general. It is local when it involves but a small area of lung; diffuse, when it affects a fairly large portion of pulmonary tissue, usually extending into other lobes; lastly, it is generalized as when there are metastases outside the lungs.

Metastasis. Metastases of lung tumor are commonly widespread. In Adler's¹² series the bronchial lymph nodes were involved in 31 per cent of the cases, the mediastinal nodes in 12 per cent, cervical lymph nodes in 6 per cent and the tracheal lymph nodes in 7 per cent of the cases (50 per cent for all lymph nodes). The liver was involved in 26 per cent, the pleura in 13 per cent, kidney in 15 per cent, brain in 13 per cent, heart and pericardium in 18 per cent, adrenals in 10 per cent and the bones in 15 per cent of the cases. In order of the frequency they are: (1) Regional lymph nodes; (2) liver; (3) heart and pericardium; (4) kidneys; (5) abdominal lymph nodes; (6) pleura; (7) brain; (8) bones, where it may be widespread ribs, spine, skull and sternum are involved in the

order named. I cannot find any figures as to the frequency with which inguinal and axillary glands are involved. Approximately 25 per cent of the cases show no metastases at autopsy.

Case Reports. CASE I.—Hospital No. 42092. A male, aged forty years, who was admitted to the Lebanon Hospital, October 4, 1923, with the following complaints: Pain and swelling of small joints of hands and feet, fever and headache, and cough.

About four months prior to admission pain, swelling, redness and stiffness of hands and feet appeared. At the same time, he had headaches, some general weakness, and loss of appetite. Loss of sexual power and constipation became manifest within two weeks before admission, and he sought admission chiefly because of pain in hands and feet and loss of sexual power. The patient did not think that he had lost weight.

Physical Examination. General appearance was that of a fairly well developed, but anemic looking, man. The head was negative. The neck showed fairly large masses of glands in both supraclavicular regions; there was considerable edema about the tissues at the base of the neck. There was no evidence of inflammation about these supraclavicular masses.

The lungs showed diminished expansion in the right side, with flatness in the upper two-thirds of the right lung, both anteriorly and posteriorly, and dulness at the base. The breathing was distant bronchial, with a distinct cavernous quality to the expiration. At the left apex there was dulness, and the breath sounds were distant bronchial. There were no rales heard. The abdomen was negative. The extremities showed the joints of both hands, and feet were red, tender and stiff and swollen. This was especially well marked at the metacarpophalangeal joints. The distal phalanges were thickened and showed the changes usually associated with pulmonary osteoarthropathy. The reflexes were normal.

The temperature was 101° F.; respiration, 24; pulse, 100; weight, 135 pounds; blood pressure, 106/36.

Laboratory examination showed: Blood: Hemoglobin, 68 per cent; red blood cells, 3,600,000; leukocytes, 13,000; polymorphonuclears, 80 per cent; lymphocytes, 20 per cent. The blood Wassermann, sputum, stool and urine were negative.

The roentgen-ray showed a dense irregular shadow occupying the upper two-thirds of the right lung, obliterating all the marking. This could either be an effusion or a neoplasm. The pathological report on a small supraclavicular node removed soon after admission was adenocarcinoma.

Clinical Course. While under observation in the hospital the temperature ranged between 99.5° and 101.5° F. Weakness and anemia became marked, and loss of weight was very noticeable.

Enlarged axillary glands appeared about October 12, first on the left side and then on the right. These persisted and became larger. The cough became more persistent and productive; his appetite became very poor and his joint pains did not clear up. He lost ground steadily, and on November 2, 1923, his family removed him to another institution against our advice, where he died, several hours after admission. There, an incomplete necropsy showed, in addition to an extensive right lung and pleural involvement with adenocarcinoma, the presence of a considerable sanguine purulent effusion into the right pleural cavity.

CASE II.—No. 85663. B. S., a male, aged sixty-seven years, was admitted, November 7, 1923. He was discharged, November 28, 1923, with a negative family history and a negative previous history.

The patient came into the Lebanon Hospital, complaining of cough and dyspnea, hemoptysis, loss of weight and weakness, which began about three months ago with a cold in nose and throat, lasting three days. The cough developed soon after the head cold, and was productive of a whitish sputum. There was some pain in the left chest and moderate dyspnea about the same time. The cough was not distressing until about four days before admission, when sputum was blood-streaked and remained so up to admission. Dyspnea was very marked by now. Patient stated that he lost 30 pounds in weight since onset of cough and dyspnea.

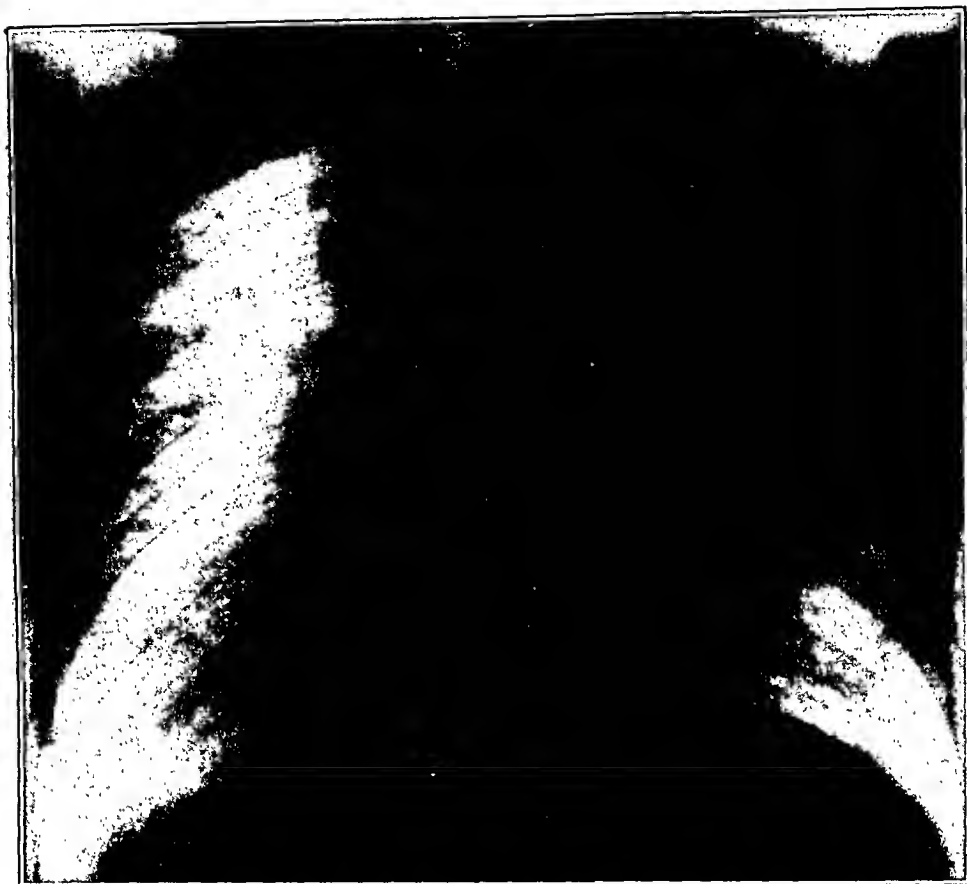
Physical Examination. This showed an emaciated and weak-looking old man, sitting up with an effort and breathing with difficulty.

The chest showed retraction of supraclavicular and infraclavicular as well as intercostal spaces. This was more pronounced on the left side.

Over the entire left chest expansion, fremitus and the breath sounds were very much diminished. The breath sounds, however, were of a distinct cavernous quality, best heard with the naked ear. The percussion note was flat on the left side from the apex downward, except at the very base where it was dull. The right side showed exaggerated breath sounds, with prolonged expiration throughout. There were a few scattered rales over the right base. The rest of the examination was essentially negative.

The temperature was 101.2° F. on admission, but soon became subfebrile, and during the second and third week of the hospital stay it was fairly normal, even though clinically the patient was much worse.

Laboratory Examination. Blood: Hemoglobin, 68 per cent; red blood cells, 3,500,000; leukocytes, 10,500; polymorphonuclears, 82 per cent; lymphocytes, 18 per cent. The blood Wassermann, sputum and urine were negative; blood chemistry was normal;



CASE. I.—Massive involvement of right lung, with patient never complaining of any symptoms referable to respecting system. The glands in both supraclavicular region when markedly enlarged and patient had marked osteoarthropathy.



CASE II.—Diffuse involvement of left side and nodular infiltration on right side with rapidly progressive course.



CASE III.—Hilus involvement with onset of pain in gluteal region.

blood-pressure, 130/70; phenolsulphonephthalein test: 13 per cent first hour and 12 per cent second hour.

Roentgenogram: Dense shadow involving whole left pulmonary field. The density is less in the apical region. There were numerous miliary infiltrations studding the upper two-thirds of the right lung, becoming conglomerate along the middle third about hilum. The trachea is pulled to the left.

Conclusion. A probable new growth in the left lung, with miliary metastasis in the right lung.

Clinical Course. He grew perceptibly worse insofar as his dyspnea increased; cyanosis became permanent. He developed periods of orthopnea. His sputum was profuse and at times blood-tinged. It was repeatedly negative for tuberculosis. He left the hospital on his own responsibility, November 28, 1923, in rather poor shape and died three weeks later.

CASE III.—M. D., a male, aged forty-nine years, was admitted to the Lebanon Hospital, November 26, and was discharged, December 12, 1923.

The family and previous history was negative. He was admitted complaining of pain in the left buttock and the left leg and slight cough. Four weeks before admission he was suddenly seized with pain in the right iliac region and in the right side of the abdomen. Soon thereafter he began to have pain over right lower costal region. The pain was in the nature of an ache, continuous, but aggravated on motion and worse at night, causing loss of sleep, and only relieved by narcotics. This lasted about ten days, when the pain in the leg and abdomen gradually let up, but the pain over the lower left chest became more intense. About this time a cough appeared, and following the appearance of the cough he developed pain in the left leg, especially in the mid-tibial region which was tender. This left-leg pain was quite severe, and persisted up to admission. During the month preceding admission he lost his appetite, became constipated, had an occasional night-sweat and some pain on urination. The patient did not think that he had lost weight.

Physical Examination. The patient was a pale and moderately emaciated man who was more or less apathetic, as if in pain. The head, neck and chest showed nothing abnormal. There was some tenderness in the right upper abdomen and lower costal area (tenth and eleventh ribs). This tenderness appeared to be rather superficial, unlike the pain due to involvement of an abdominal viscus. Deep pressure over the ribs, however, caused exquisite tenderness. There was also some tenderness over the vertebral spines from the first to the sixth dorsal spine and over the mid-tibial region. The rest of the examination, including a routine neurological examination, showed no other abnormalities.

The temperature on admission was 99° F. and rose to 101° F. soon afterward, and during observation the temperature varied between 99° and 102.4° F.

Laboratory Findings. The blood showed a moderate anemia; the urine showed a trace of albumin with an occasional hyalin cast. The blood chemistry was normal. The Wassermann on the blood was negative, and the spinal fluid Wassermann was weakly positive. The stomach content after an Ewald meal was normal.

At this junction no diagnosis was ventured, and it was decided to resort to roentgen-ray study of the gastro-intestinal tract and the osseous system. To our surprise, while studying the ribs, on December 1, 1923, a dense irregular shadow was seen to occupy the region of the right hilum infiltrating the adjacent pulmonary tissue. There was no abnormality seen in any of the bones studied (tibia, iliacs, spine and ribs). The roentgenologist (Dr. J. Bower) concludes that there was definite evidence of primary neoplasm in the lung.

Peculiarly enough, even after the roentgen-ray evidence of right-lung involvement, the clinical examination yielded no physical signs. About a week afterward, however, an area of diminished breathing just above the right base posteriorly extending from the spine to the axilla was recognized. Dulness appeared over the same area about the middle of December, six weeks after the onset of illness. About this time a mass was felt in the right upper quadrant, which was thought to be possibly due to metastatic involvement of the liver. A roentgen-ray examination of the iliac region this time showed some areas of rarefaction, probably due to metastasis.

While under observation in the hospital the patient developed prolapse of the rectum, causing him a great deal of distress. He lost ground for a while and then remained stationary, except for the cough which was more or less progressive. He also lost considerable weight. On December 19, 1923, he was removed to another institution for deep roentgen-ray and radium therapy. He was heard from about four months later, when his condition was said to have somewhat improved under treatment.

Discussion. A perusal of the above clinical histories leads one to the belief that pulmonary neoplasm is not always manifested early by symptoms referable to the lung. In but one of the cases (Case II) did the patient complain of cough early in the disease. In another case the pain due to metastasis evidently appeared much before one suspected the lung affection. These facts forcibly emphasize the importance of complete clinical and laboratory investigations, when symptoms and signs are not explicable on an obvious basis. To be sure, a diagnosis of pulmonary neoplasm may not be made on insufficient data, but suspect it one may, and in order to rule it out will require complete laboratory and clinical study.

The role of infection, and more particularly influenza with the resultant epithelial proliferation and atypical metaplasia as a possible source of irritation, is mentioned and stressed by many authors. Moise,¹⁷ in a comprehensive study of 5 cases, is inclined to that belief, and Winteritz and McNamara,¹⁸ both from a study of the pathology of influenza and from experimental data, are led to the same view. Surely there is an evident increase in the number of cases of lung tumor in the past five or six years. However, fascinating as theorizing about the subject as to the genesis of tumor of the lung may be, it must be admitted that the evidence so far adduced indicating influenza, even as a contributory cause, is but circumstantial in nature, and can therefore not be regarded as convincing from a scientific standpoint. For the incidence of cancer elsewhere, which is also admittedly increasing according to mortality tables and reports from life insurance sources, is more easily explained on a basis of better diagnosis, and more correct death reports in general, rather than on a basis of some particular phenomenon, such as the influenza epidemic. Further studies along experimental lines, once the true etiology of influenza is found, may prove more fruitful. At present one can but guess at the cause of cancer anywhere in the body.

Summary. A report of 3 cases of primary pulmonary neoplasm is presented, together with a discussion of the increased frequency of this disorder.

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INTERMITTENT COMPLETE HEART-BLOCK AND VENTRICULAR
STANDSTILL.

BY LESLIE T. GAGER, M.D.,

AND

HAROLD E. B. PARDEE, M.D.,

NEW YORK.

(From the Electrocardiographic Laboratory of the New York Hospital.)

THE observation of a patient who at times had complete heart-block, with Adams-Stokes attacks due to ventricular stoppage, and at other times a normal heart beat with a normal auriculoventricular conduction time, seems worthy of reporting. Especially is this so since we were able to secure electrocardiographical records of the cardiac mechanism preceding and following the attacks. Moreover, the occurrence of intermittent complete heart-block and syncope, with normal conduction between attacks, has been recorded so rarely that Carter and Dieuaide,¹ in describing a case of their own, collected only eight definite instances in the literature. The case which we wish to report corroborates certain of the physiological facts associated with the Adams-Stokes syndrome, and illustrates in a striking manner the effect of digitalis in precipitating these syncopal attacks, in the presence of a block already complete.

Case Report. S. B., aged fifty-nine years, white, occupation a checker, was admitted to the First Medical Division of the New York Hospital, the service of Dr. Lewis A. Conner, on December 23, 1919, complaining of weakness, dizziness and fainting spells.

The family history was negative, and the patient recalled no infectious diseases, except gonorrhea without complications. In particular, there was absence of cardiorespiratory symptoms of disease.

The onset of the present illness was two weeks before admission, with weakness and palpitation. Two or three times a day fainting spells began to occur, with loss of consciousness for periods of two to three minutes. Such attacks were preceded by weakness and dizziness, and the patient found if he lay down at the beginning unconsciousness did not ensue.

Physical examination on admission disclosed a well developed and well nourished man, lying in bed without dyspnea. There was slight cyanosis of the lips and face. The jugular veins were distended, and their pulse rate was rapid, 100 per minute. The apex rate was 26, with a regular rhythm. Relative cardiac dullness extended 12 cm. to the left in the fifth interspace, and 4 cm. to the right in the fourth interspace. In addition to the heart

sounds, which were normal, there could be heard, inside the apex, faint, short, muffled sounds, sometimes two and sometimes three, in each diastole. There was a faint blowing systolic murmur at the apex. There was no pulse deficit. The peripheral arteries were markedly sclerosed, and the blood pressure was 140/75. The abdominal organs were not felt, there was no edema and pupillary reactions and tendon reflexes were normal. The Wassermann blood test was negative; the blood picture was normal, with hemoglobin 85 per cent, and the urine contained a faint trace of albumin.

Subsequent Record. Three attacks of syncope were observed on the day of admission, with dyspnea and stertor, pallor, loss of consciousness, and general muscular spasticity. No further attacks occurred during the following week, the ventricular rate ranging from 24 to 32 beats, with a rise on two occasions to 44. The treatment during this period was rest in bed, with atropin (gr. $\frac{1}{100}$), by mouth, four times a day.

On December 31, atropin was discontinued and standardized tincture of digitalis was given (0.65 cc per cat unit), 1 dram at 4 P.M., a second dram at 6 P.M. At 12.20 A.M., on January 1, the patient had an attack of dizziness, lasting ten minutes. At 9 A.M. was seen the first syncopal attack since the day of admission. At 11.30 A.M. four attacks occurred during fifteen minutes, and in the afternoon the paroxysms became more numerous, the use of atropin being without effect. The duration of these attacks was usually from thirty to sixty seconds. There would be a period of ventricular asystole of from six to twenty seconds, then the fit, with the gasping for breath, agonal expression, rolling of the eyes, extreme pallor and syncope of varying duration, followed by return of the pulse, with flushing and sweating. During one series of frequent attacks the radial pulse would come back at a rate of about 72, would suddenly cease, a fresh spasm ensue, and so on quite continuously until the reestablishment of a ventricular rate of 20 to 24 per minute. The blood pressure on January 2 was 144/70.

Another dram of tincture of digitalis was given on January 3. The attacks diminished in frequency and ceased on January 5. On January 6 an electrocardiogram showed 2 to 1 rhythm to be present. Right vagus pressure caused an increase of this block to a higher grade. There was a slight attack on January 7. The pulse-rate rose to 60 to 64 beats per minute at the wrist on January 11, and a record on January 16 showed that normal conduction and rhythm were present. The blood pressure was 150/70. On January 24 the patient was discharged with normal rhythm and free from symptoms.

After working without incident for nearly five months the patient, on June 19, had two short attacks, marked by dizziness, weakness and "flushing in the fingers," without loss of consciousness. He

came into the hospital on June 24, with a ventricular rate of 42 and a venous pulse rate of about 90. On June 29 occurred three slight attacks for the first time since this admission, and notwithstanding a second negative Wassermann test, because of the positive venereal history, 0.2 gm. of neoarsphenamin was given intravenously. Three hours later, at 6 P.M., a series of attacks began which continued throughout the night and the next day, at the rate of two to three an hour. On July 1 the paroxysms were almost continuous, but following the intravenous injection of adrenalin (15 minims, 1 to 1000) the ventricular rate rose to 66, and after two or three short paroxysms they ceased entirely for one and a quarter hours.

On July 2, following adrenalin, the ventricular rate became 66, with a pulse of good quality, and regular. Suddenly the pulse became irregular and almost imperceptible at a rate of about 100. The patient became pale with labored breathing, and the presence of ventricular fibrillation was suggested by the irregular faint heart sounds. The cessation of the pulse cut short this condition, a typical convulsive attack occurred, and these continued until the patient became permanently unconscious and died, July 3.

Necropsy. At the necropsy, performed by Dr. R. G. Stillman, the heart, which weighed 425 gm., was found firmly contracted. The left auricle was dilated and was lined by an endocardium thickened, white and smooth. The segments of the mitral valve were thickened and contracted, and the chordæ tendineæ were shortened. There was a calcified ring about the left auriculo-ventricular orifice for about three-quarters of its circumference. "The muscle is firm and presents no focal lesions, but is rather more yellowish in color than normal, and appears as though there were some increase of fibrous tissue in it." The aorta was not enlarged. The coronary and larger arteries were moderately atheromatous, but there was no narrowing of the lumina of the former.

The conduction system showed no gross abnormality, though the calcified ring must have lain in close proximity to it. Unfortunately, the conduction system was not examined in serial sections. The sections of ventricular muscle showed no abnormality. It is possible and probable that the calcareous changes around the mitral orifice had involved the bundle.

Electrocardiographical records of this patient were made at intervals from the day of his first admission to shortly before his death. They show complete heart-block and the transition through 2 to 1 rhythm to a state of normal conduction, and later the recurrence of the complete heart-block. Electrocardiograms illustrating these phases are reproduced. Fig. 1, secured on admission, shows complete block with the auricular rate 92, and the ventricular rate 27, per minute. The prolongation of systole to 0.64 second is note-

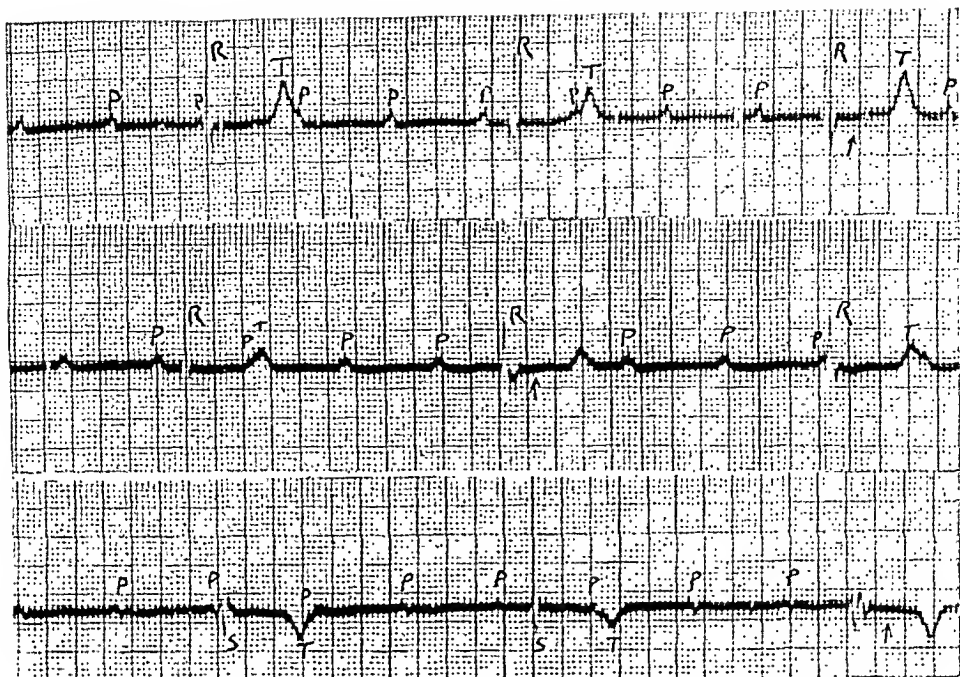


FIG. 1.—Record on admission showing complete heart-block.

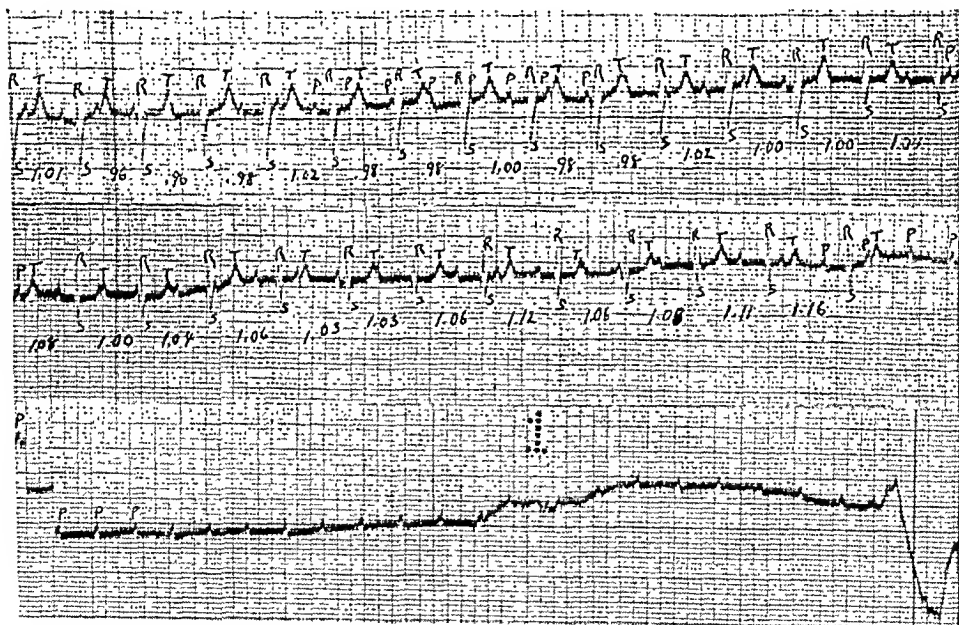


FIG. 2.—Record of January 3 showing paroxysmals of ventricular tachycardia with complete heart-block, followed by ventricular stoppage. This record is by Lead I and the three parts of it are continuous from above downward, overlapping slightly as can be seen. The figures are the duration in seconds of each interventricular interval. The large movements at the end of the record are due to the onset of a convulsion.

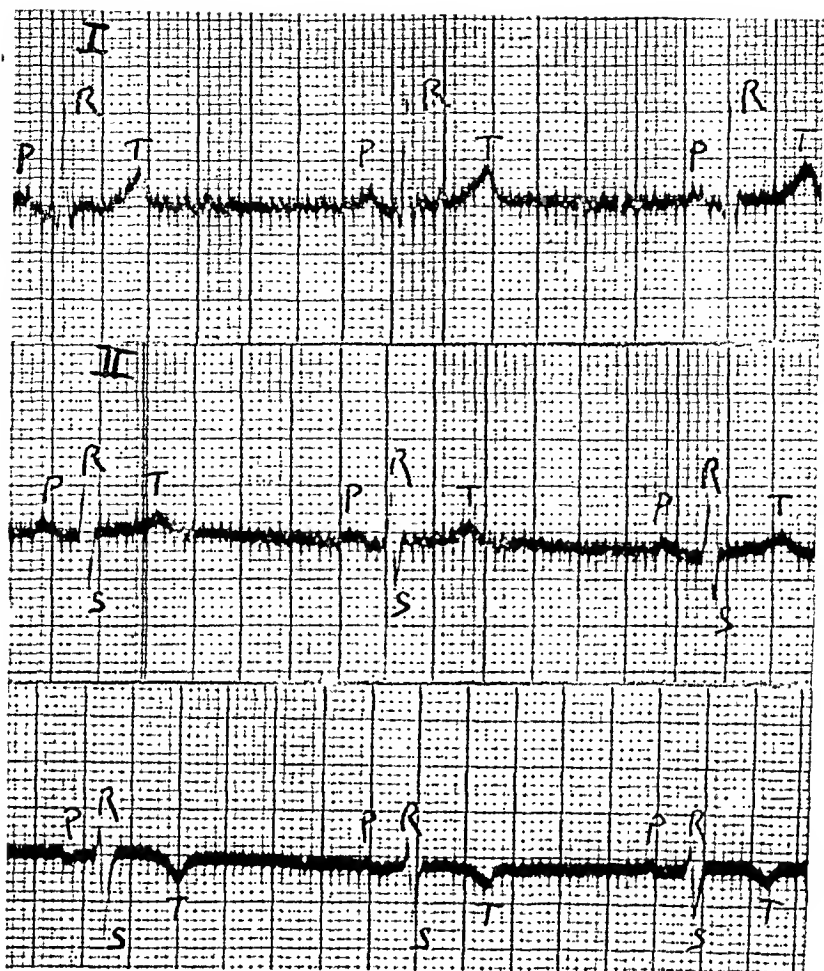


FIG. 3.—Record of January 16 showing normal A-V conduction time, the P-R interval measuring 0.18 second.

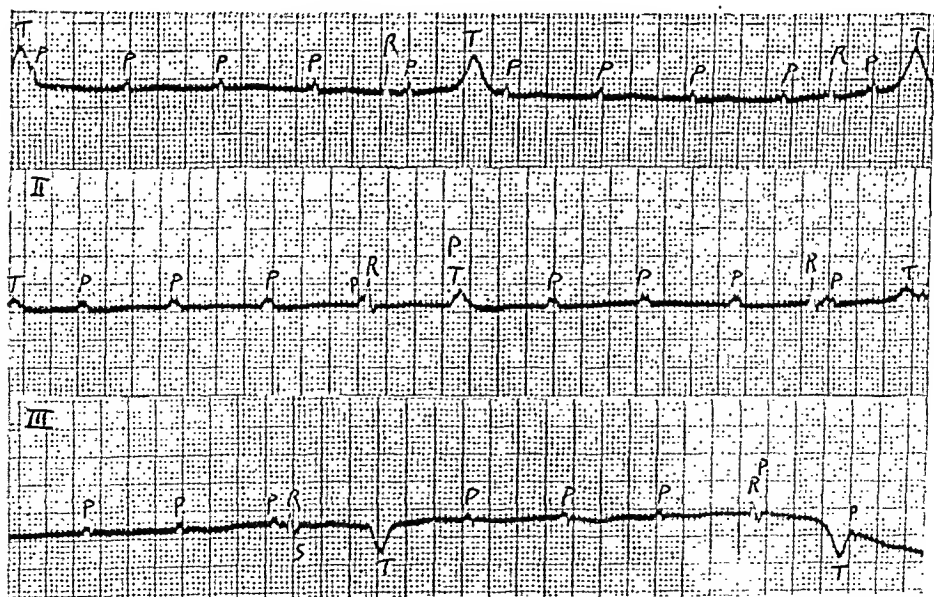


FIG. 4.—Record of January 29 showing complete heart-block with a very slow ventricular rate, about 18 per minute.

worthy, but is common with such slow heart rates. The $Q-R-S$ group has a duration of 0.12 second, but the presence of the supra-ventricular form indicates that the impulse, as is usual with complete heart-block, arises from the $A-V$ node or at least from a part of the $A-V$ bundle above its branching. During this record the ventricular beat is quite regular, but on January 2 records were obtained with an irregular ventricular action of about 15 to the minute. The pauses between beats were sometimes as long as six or eight seconds and varied irregularly. At the same time, the auricles were regular at 94 per minute. The ventricular waves, as in Fig. 1, showed an origin in the $A-V$ node or bundle.

Fig. 2, taken on January 3, when frequent paroxysms were in progress is of particular interest as showing the cardiac mechanism before the attack. The first portion of the record, which is by Lead I, shows ventricular tachycardia. The ventricular rate is 60; the auricular rate is 100. Both chambers are regular in rhythm. At the fourteenth beat there is a change in the form of the ventricular complex. The duration of the $Q-R-S$ group diminishes from 0.14 second to 0.12 second and later to 0.1 second, and the form of the waves comes to resemble more nearly the usual complexes of this lead as seen in Fig. 1. Both the $Q-R-S$ and the T waves are changed. The diastolic interval lengthens irregularly as this change in the form of the waves takes place, and finally, after two still longer pauses, the ventricles cease beating. The gradual decrease in the irritability, along with a change toward the normal in the waves of the ventricular contractions, suggests that the stimulus for the heart beat is changing its location from a point in the (right?) ventricle to a point in the $A-V$ bundle above its branching.

This lengthening of the diastolic interval with change in location toward the $A-V$ node was observed in the other records of this patient which showed the cessation of the ventricular beat. It would seem that the $A-V$ node at this time was unable to maintain a spontaneous beating, and only when the ventricular centers took over the function of stimulus production could the heart beat be maintained. The lowered irritability of the node which caused the slow irregular beating on January 2 had now given way to a complete depression of irritability.

The attacks ceased on January 5, and on January 6 a record showed partial heart-block, the auricular waves being followed alternately by a normal conduction interval (0.16 second) and by a failure of conduction. This 2 to 1 block continued for several days, and Fig. 3, taken on January 16, showed a normal heart beat, 60 per minute, with normal $A-V$ conduction time (0.16 second). A change in the T wave was seen as might have resulted from the 3 drams of tincture of digitalis which were given on January 1 and 3. It has disappeared in Fig. 3, which shows

ventricular waves like those of Fig. 1, except that there is a more definite left ventricular predominance.

On April 1 the patient returned for a record which was quite similar to Fig. 3 and showed normal conduction.

Fig. 4 was taken on June 29, during his second admission, on the day he began the series of attacks that proved fatal. Complete heart-block is present, the auricular rate being 85 per minute, while the ventricles beat regularly at 19 per minute. The small size of the *Q-R-S* group in all leads of this record is probably due to a poor physiological condition of the muscle. There was no significant difference in blood pressure whether complete heart-block (excluding, of course, the time of attacks) or partial block or normal rhythm was present, and the size of the *T* wave during periods of complete block, compared with its amplitude during normal *A-V* conduction, indicates the more forceful ventricular contraction associated with the slower rate.

Discussion. The clinical interest of this case attaches to the intermittent complete heart-block with normal *A-V* conduction intervening, and to the periods of ventricular standstill, during which the patient exhibited all of the usual sequelæ of such attacks: the sensation of flushes in the fingers and other parts accompanying momentary cessation of the beat; the loss of consciousness which commonly, though not always, occurs when stoppage lasts more than two to three seconds, and finally the epileptiform seizures that supervene after asystolic periods of from fifteen to twenty seconds' duration. In the reported cases there have been wide variations in the duration of standstill before convulsions occur. In the record from our patient taken on January 2, when the ventricular action was very slow and irregular, the waves characteristic of muscular spasticity appeared after six seconds of ventricular stoppage. At the other extreme, in a patient reported by Wiltshire,² periods of standstill up to sixty-seven seconds occurred without convulsive movements. The most prolonged duration of ventricular stoppage so far reported was for one hundred and thirty seconds, which was observed in the patient of Stengel,³ and in this case convulsions occurred.

Of paramount importance is the opportunity to analyze the electrocardiographic records of ventricular stoppage in man, for, naturally these are still rare, though the phenomenon has been recognized for a full century. The polygraphic records that have been secured from time to time have thrown much light on the physiology of ventricular stoppage, but particularly important observations on ventricular standstill in dogs have been made by Erlanger and Hirschfelder⁴ in the course of experiments upon the mechanical production of heart-block. Their conclusions were that stoppage could be produced in four ways: (1) By inhibition of the auricles through vagus stimulation, while the conduction

system is intact; (2) in the presence of partial heart-block, by an increase in auricular rate, which produces fatigue of the *A-V* bundle; (3) by a compression of the bundle sufficient to produce complete heart-block; (4) in the presence of total heart-block, by the sudden cessation of fairly rapid rhythmic ventricular stimulation. The underlying cause in each case is the lack of the usual stimulus to contraction, no matter whether this is ventricular or supraventricular. The ventricle then remains in standstill until its dormant pacemaker again begins to function.

In the case here reported the evidence suggests that the ventricular stoppage was due to variations in ventricular rhythmicity. The changes in the form and in the duration of the ventricular complex of the electrocardiogram immediately preceding the periods of ventricular standstill are proof of corresponding changes in the pathways of intraventricular conduction, and, by inference, in the site of origin of the impulses. It is reasonable to suppose that the ventricular tachycardia depressed the irritability of the ventricles and brought about the inactivity of one pace-making center after another until stoppage resulted.

It always demands careful study, however, to properly estimate the importance of these various physiological mechanisms in specific instances of ventricular standstill. In Starling's patient,^{5,6} for example, vagus stimulation alone was responsible for the lapses of ventricular beats. Erlanger⁷ constantly noted auricular acceleration in his patient immediately before the ventricular silence. In the patient observed by Earnshaw,⁸ and by Thayer and Peabody,⁹ diminution of ventricular irritability appeared to play the predominant role, though vagus action on the auricles and a partially defective function of the *A-V* bundle were also regarded as factors. In the case reported by Wilson and Robinson,¹⁰ a rapid idioventricular rate and the resulting depression of ventricular irritability, seemed to be the most important factors, but they considered that a disturbance of auriculoventricular conduction was also a factor. An example of a purely mechanical production of heart-block and ventricular standstill is reported by Lewis¹¹ in a case where engorgement of large blood sinuses in the *A-V* bundle caused the attacks.

It is evident that any of the several mechanisms discussed by Erlanger and Hirschfelder⁴ may be operative in different patients, and it will always be a nice study to decide in each case. As Lewis¹² says, "The solution of the problem of the fits of complete heart-block rests with the investigation of the influences which increase or decrease the idioventricular rate," and to this end the information of the electrocardiographical record must be correlated with accurate clinical data.

Summary. A case of intermittent complete auriculoventricular heart-block is reported.

Syncopal attacks during the complete block are found to be due to ventricular standstill, varying from six to twenty seconds' duration. Such attacks followed the administration of digitalis.

The physiological factors bearing on cessation of the ventricular beat are discussed, and it is concluded that in this instance changes in nodal and ventricular rhythmicity appear to be the governing factor in producing standstill, while definite vagus and auricular influences are absent.

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GOITER HEART.

BY NELLIS B. FOSTER, M.D.,

NEW YORK.

It is now generally believed that thyrotoxic states, whether induced by exophthalmic goiter or by toxic adenoma, are characterized by an abnormal increase of oxidation in the tissues. This increase of oxidation is what we attempt to measure and to express in terms of basal metabolism. By this increased consumption of oxygen, the patient with Graves disease is on a physiological plane with the normal individual who is doing hard muscular work. Physical exercise increases the consumption of oxygen and elevates metabolism, and the same is true of febrile states. When the tissues require more oxygen, the work of transporting it from the lungs to the tissues falls upon the heart; therefore, other things being equal there is rapid heart action during severe exertion, with pyrexia and, in general, whenever there is an elevated metabolism. Thus considered it becomes evident why abnormal states of metabolism may be accompanied by disorders of heart action, or, if these states be prolonged into chronicity, by actual myocardial degenerations.

The toxic state of hyperthyroidism may be induced by the classical type of exophthalmic goiter, or equally well by the less striking clinical syndrome of adenoma of the thyroid. In fact the two syndromes not rarely merge, one into the other, with a result that cases

of toxic adenoma with exophthalmos are regarded as true exophthalmic goiter. Differentiation is an attempt to harmonize clinical syndromes with anatomical lesions, an attempt which in this instance is often possible; but there are striking exceptions. In essentials the cardiac disorders secondary to exophthalmic goiter are the same as those associated with toxic adenoma. But since the latter disease is apt to develop somewhat later in life the damage to the heart in cases of adenoma is more likely to be serious and permanent than with exophthalmic goiter. Complete irregularity of the pulse is commonly held to be evidence of a grave cardiac lesion, and this may be the case; but this irregularity, even when associated with symptoms which suggest circulatory embarrassment, is hardly a criterion of organic heart disease since a permanent reversion to normal rhythm can so often be induced.

Cases of thyrotoxicosis, of whatsoever causation, are prone to have symptoms suggestive of cardiac disease. Besides the usual tachycardia, these symptoms are palpitation, pain and dyspnea. These symptoms may be present when there is no detectable evidence of cardiac disease—indeed in cases where the subsequent history is of such a character as to exclude cardiac disease. Statistics are of little help in formulating judgment concerning a concrete case; but it is probably conservative to estimate that over half the cases presenting symptoms have no significant organic lesion. There are too, other reasons than symptoms alone which may lead to mistakes in diagnosis. Not infrequently in milder degrees of thyrotoxicosis the apex impulse has a slapping quality and there is a prolongation of the first sound closely resembling a murmur. When these signs accompany symptoms, it is easy to understand why the case may have been regarded as one of mitral stenosis. The error is most likely to occur when the evidences of thyroid disorder are latent and obscure. Sometimes there are signs suggestive of aortic regurgitation. In toxic thyroid states the systolic blood pressure is either normal or slightly elevated while the diastolic is low on account of the vasodilation of the arterioles. This constitutes a high pulse pressure notable in the radial as a pulse of water-hammer or Corrigan type.

There is quite a different syndrome, which on account of the pre-eminent symptoms being of a vascular character, not infrequently simulates hyperthyroid states. When neurocirculatory asthenia occurs in a young woman who also happens to have an adolescent goiter, the resultant impression is apt to be that of thyroid disease. More or less constant tachycardia, dyspnea on exertion, some tremor; these are the usual symptoms and examination of the heart often reveals a slight thrill, with systolic shock and possibly a prolonged first sound which is almost a murmur. The identical symptoms and signs are often noted in young individuals of somewhat asthenic type and are correctly interpreted as not related to any organic

cardiac disease; but when there is also a visible thyroid enlargement, it seems to prejudice judgment and due weight is not given to conflicting evidence. The subsidence of this tachycardia during sleep is one of the helpful means of differentiation.

The commonest type of cardiac disorder accompanying thyrotoxicosis is auricular fibrillation, detectable on account of the complete irregularity of the pulse. Arrhythmias induced by numerous premature systoles, or by flutter are less frequent. In early cases of exophthalmic goiter there may be periods of auricular fibrillation followed by periods when the pulse reverts to a normal rhythm. In fact it is probable that persistent fibrillation is usually preceded by paroxysmal fibrillation. Now these complete arrhythmias are credited with an ominous significance which is far from correct. While fibrillation of the auricles may be one of the signs of a failing heart, it is equally true that complete irregularity is not incompatible with years of arduous life. But the chief consideration in its relation to thyroid disease is that this type of cardiac disorder increases to a marked degree the danger incident to any operation. For reasons which are not entirely clear, mural thrombi are prone to form in the fibrillating auricles and following operations detached portions of these thrombi occasionally produce embolism and infarctions. This is also a danger if quinidin be carelessly employed.

Why the heart is especially liable to this peculiar arrhythmia in hyperthyroid states is a matter of conjecture largely, probably the low vagus tone which characterizes the primary disorder is an important factor. Whether there is also a lesion of the myocardium which might be a predisposing factor is not definite. There is evidence for such an idea both in the character of the lesions found at autopsy and likewise of the lesions which may be produced in animals by feeding thyroid substance. It is difficult, however, to interpret correctly the lesions found in the human heart in cases of thyrotoxicosis. That the myocardium in such cases presents evidence of degeneration has been noted repeatedly. Fatty degeneration, perivascular round-cell infiltration, sometimes focal necroses, these have all been described. But these are not unusual lesions in various chronic diseases, which occur in middle life and they are perhaps especially common in association with simple, non-toxic goiter. In order to indicate a direct relationship between these lesions and hyperthyroid states, it would be necessary to show that myocardial degenerations of these types are very much more common in cases of thyrotoxicosis than in other cases dying at the same age periods, also it would be necessary to exclude other possible causes for the lesions. There are at present no statistics on this subject. Color of plausibility is given to the conception of myocardial degeneration being produced by thyrotoxicosis by experiments on animals. Perivascular infiltration and focal necroses have been found in animals following periods of feeding thyroid

substance or the injection of thyroxin (Hashimoto, Goodpasture). Possibly quite as important is the observation that the heart of an animal thus treated appears to be more vulnerable to some toxic agents (that is, chloroform) than the normal heart. Perhaps it is not so much the increased activity of the thyroid which affects the injury, but rather that the intoxication produces a condition in the myocardium which predisposes it to injury from minor infections. Should it be possible to demonstrate foci of degeneration in the hearts of persons dead of thyrotoxicosis, this fact would help to explain the predisposition to auricular fibrillation already mentioned. Experimentally, fibrillation is easily produced by faradization of an area in the auricles and the current theory in explanation of fibrillation assumes foci of degeneration in the auricular myocardium.

It has often been noted that the heart in cases of thyrotoxicosis is enlarged. Because there is such an evident demand upon the heart in this disease, it has been assumed that the enlargement is due to hypertrophy. Marine and Lenhart expressed this idea in suggesting that the goiter heart is a result of work hypertrophy. Just what an elevated metabolism means in demand for increased cardiac effort deserves consideration. In thyrotoxic states the increase in basal metabolism is often of such a degree that the patient when at rest is on a physiological plane with a normal person engaged in hard exercise. Physical exercise increases basal metabolism. Elevated metabolism, whether normally induced by physical exertion or abnormally induced by intoxication means increased oxygen consumption. Boas has calculated that in the thyrotoxic patient one-quarter again as much oxygen must be transported from the lungs to the tissues as in a normal person. The chief means for this accomplishment is by increasing the rate of the circulation. The increased minute-volume flow in exophthalmic goiter was demonstrated by Plesch some years ago and he estimated that it amounted to about 50 per cent. This increase is effected apparently largely by rise in heart rate since there is no evidence that the systolic output is augmented. The total bloodflow in thyrotoxic states is roughly proportionate to the metabolism rate, hence an elevated metabolism must increase the work thrown upon the heart. Besides these somewhat mathematical relations, there is the factor of wastage. Plummer and Boothby have shown that the patient with toxic goiter labors under the peculiar handicap that to perform a given amount of work more energy is required than under normal conditions.

It would seem then, in view of these constantly augmented demands on the heart, that ventricular hypertrophy would be an inevitable result. This does seem to happen occasionally but not with any constancy or consistency. Of 21 cases examined postmortem (Wilson) in only 2 did the heart exceed 500 gm. in weight. An increase of 10 per cent over the theoretical normal is not enough to

prove hypertrophy. And there is now a recognized relation between ventricular weight and body weight. Lewis expresses this relation as a ratio and Hermann and F. Wilson determined this ratio in a series of thyrotoxic cases studied postmortem and found an average of 0.00292, which is similar to Lewis's figure for normal. One is forced to conclude then that while some cases may show unquestionable degrees of cardiac hypertrophy, nevertheless hypertrophy is not the inevitable result that might be expected.

The various factors which operate to produce goiter heart are confusing and in some essentials not yet understood. It is, therefore, to be expected that therapeutic measures will be somewhat in debate and that now and then someone questions the usefulness of digitalis; perhaps even holds it to be dangerous. Since the vegetative nervous system in cases of toxic goiter is disordered and the effect of digitalis on the heart is in part produced through the vagus, there will be less prompt response to digitalis in this disease than in cases of purely cardiac disease. Of ill-effects of digitalis I have seen none, and but rarely has it been impossible to restore a normal rhythm in cases of fibrillation. In the last year during which, in addition to digitalis, we have used quinidin in a manner which seems peculiar to our clinic, we have not failed to restore normal rhythm in any case of fibrillation in a goiter heart.

The risk of operation in cases of thyrotoxicosis is appreciably greater when there is auricular fibrillation. On this account especially, it is of great importance to restore a normal rhythm as a part of preoperative treatment. Then too, these sensitive patients seem to be unusually conscious of the turmoil of arrhythmia and so soon as it ceases they at once become more quiet and improve surprisingly.

No measures directed solely to treatment of the cardiac disease are likely to be successful unless combined with methods to improve the general condition of the patient. The first essential is rest, physical and mental. This is necessary in any severe cardiac disorder and is especially demanded in cases of goiter heart. The patient must be kept in bed. Sedatives are usually required, luminal or chloral are preferable to bromides because the latter upset digestion. Sufficient sleep must be secured even if morphin has to be used. The cautious use of iodine is indicated; it is often effective in reducing metabolism in exophthalmic goiter though not invariably, and sometimes in cases of toxic adenoma. When the metabolism does not subside after iodine therapy it may do so with quinin. There are scientific grounds for the use of quinin, though it has never been tested systematically in thyroid disease. In addition to these general measures the first step in attempted control of auricular fibrillation is to effect digitalization. The amount of digitalis required to do this is variable and it may be only roughly estimated as an average of 2 minims of tincture per

pound body weight. Half the theoretical amount may be given as the first dose, the remainder within forty-eight hours, according to Pardee's method. After this, digitalis should not be discontinued though the dose may be decreased, the daily amount must be determined by the pulse rate and evidence of toxic effect. In cases of thyroid disease even when there is no gross evidence of cardiac disorder a careful study of the heart is indicated, and when the electrocardiogram shows the usual characteristic abnormal *T* wave, systematic use of digitalis should be carried out, especially if operation on the thyroid is contemplated.

In some instances when the response to treatment is prompt and the metabolic rate abates considerably, there is a reversion from auricular fibrillation to normal rhythm after the use of digitalis alone. More often, however, this does not occur, at least in our experience which is apt to be with cases of considerable duration before they enter the clinic. It is with this latter group that the treatment with quinidin is so effective. In the first place quinidin cannot be expected to act on a heart which is grossly incompetent; and it is possible in such cases that its influence becomes dangerous. So long as there is edema, passive congestion of the lungs or kidneys, or a pulse deficit, quinidin, in my opinion, is contraindicated. It is contraindicated also if there is fever.

Before using quinidin it is necessary to have the patient well under the influence of digitalis. It is not always possible in cases of toxic goiter to secure the slow pulse of about seventy per minute which we strive for in cases of fibrillation due to purely cardiac disorders, but a considerable slowing is usually attainable. Whether the interesting theory advanced by Riecker of our staff is correct or not, it is certainly true that quinidin acts best on the digitalized heart. When quinidin is administered the dose should be 0.4 or 0.5 gm. every four hours, day and night. Often there is reversion to normal rhythm within twenty-four hours, then the dose may be gradually decreased. If there is no effect after a day, the dose should be doubled for thirty-six hours. I have never seen any untoward effect other than slight tinnitus and mild diarrhea. When a restoration of rhythm has been secured, quinidin should not be discontinued at once, though the dose may be reduced considerably. The drug is eliminated rapidly and it is questionable, of course, how much influence 0.2 gm. twice daily has in maintaining normal rhythm. But it has been my impression that the small dose along with the continued use of digitalis prevented further fibrillation. At least there has been a surprising success with the method, and in several instances of thyrotoxicosis fibrillation has been associated with signs of severe cardiac incompetence—dyspnea, edema and evidence of passive congestion of the kidneys. Finally one important factor cannot be disregarded, namely, time. It is sometimes necessary to treat the patient for weeks as a cardiac case before surgical

measures can be entertained; but by so doing some very gratifying results have been secured.

Summary. CONCLUSIONS. Cardiac symptoms associated with thyroid disease are of common, even usual occurrence, but these symptoms may be of pronounced severity without detectable evidence of heart disease. The so-called cardiac deaths which follow operation are seldom due to heart failure but more often to vascular failure; that is to say, there is, in these cases, a vasomotor paralysis and a widening of the peripheral vascular field notable by a sharp drop in the diastolic blood pressure, a condition similar to shock.

The commonest type of disorder referable to the heart in thyrotoxicosis is auricular fibrillation. Whether this arrhythmia is due to lesions in the myocardium or to nervous influences is not yet known. Lesions in the myocardium have been described in cases of thyroid disease and they have been experimentally induced in animals, but these lesions are not found in every case.

Heart block and auricular flutter are of exceptional occurrence and probably denote serious myocardial degeneration.

It is important to control auricular fibrillation, especially if operation be contemplated, since the mortality in cases with fibrillation is higher than in controlled cases.

A reversion to normal rhythm may be usually secured by proper treatment, which includes rest, digitalis and quinidin.

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EVENTRATION OF THE DIAPHRAGM, WITH A REPORT OF A CASE EMPHASIZING THE VALUE OF THE MOVEMENTS OF THE COSTAL MARGINS IN DIAGNOSIS.

BY EDWARD C. REIFENSTEIN, M.D.,

SYRACUSE, N. Y.

THE object of this paper is to report a case of eventration of the diaphragm, to discuss the literature in relation to the same and to call special attention to the aid given by the study of the movements of the costal margins in diagnosis.

Case Report. Mr. R., a chemist, aged thirty-seven years, complained chiefly of indigestion and insomnia. His father died of

apoplexy at the age of fifty-eight years; his mother died at the age of forty-seven years, following an operation for the removal of a tumor of the abdomen. Two brothers died in infancy, and two brothers and one sister are living and well. He has been married four years, and is the father of two children. His wife is living and well. He had the usual diseases of childhood, including scarlet fever, and suffered from frequent attacks of tonsillitis during 1922. There is no other history of infection, and venereal disease is denied.

The patient denies the use of alcohol to excess. He smokes two cigarettes a day. He has three regular meals a day, and does not eat between meals or on retiring. Sweets are not taken to excess. Four glasses of water, two cups of coffee and one cup of tea are taken daily. He voids four or five times a day, but has no nycturia, dysuria or hematuria. His sexual life is normal. For the past eleven years at various times he has had indigestion, preceded by constipation and characterized by discomfort in the abdomen just above the umbilicus, which occurred from fifteen minutes to one hour after meals. This discomfort, which was not painful, but seemed due to pressure, was followed by a diarrhea of two or three movements of a soft consistency without blood or mucus. These attacks occurred once or twice a month, and appeared to be related to an increase in his mental responsibilities or if he worried.

At no time was there vomiting, and the attack usually disappeared spontaneously. His appetite remained good, there was no loss of weight or jaundice, and during the interval he was free from discomfort. He has always been considered nervous, in that trivial things worried him, and any increased responsibility made him more irritable. At these times he suffered from depression, melancholia and insomnia; otherwise his sleep was undisturbed. There has been no disturbance of the special senses, numbness of the extremities, or headaches. At no time has there been any cough. Since childhood he has been conscious of dyspnea, so that he never was able to do what other boys did without shortness of breath and exhaustion. The dyspnea has not increased in severity and is brought on by exertion. He considers the discomfort in the abdomen, the increased irritability and the insomnia, all definitely related to each other.

Physical examination showed a pale and somewhat emaciated man, weighing $132\frac{1}{2}$ pounds, and $68\frac{3}{4}$ inches tall. He had a good growth of hair on the scalp, eyebrows, chest, abdomen, axilla, forearms and legs. There was a small area of pigmentation on the right shoulder; the skin was otherwise clear. The thyroid was not enlarged. The tonsils were buried; considerable secretion was expressed from the left one. The tongue and the sinuses upon transillumination were normal, and the teeth were in good condition. There was no exophthalmos, and no von Graefe, Stellwag or

Moebius signs. The abdomen was normal to inspection and palpation. The chest was of the flat type, and the left supraclavicular and infraclavicular regions were more sunken than the right. Anteriorly above the expansion was equal on both sides. The upper and lower costal margins on the left side moved outwardly more than the right side. The right side was normal to percussion and auscultation anteriorly and posteriorly. The left side on percussion was found high pitched posteriorly from the fourth dorsal vertebra to the top. At the left base modified tympany was obtained. There was found excursion of the left diaphragm from the eighth to the ninth dorsal vertebra on deep inspiration. Tactile fremitus was retained. The breath sounds were normal and no rales were heard. The following day the same movements of the costal margins were found; percussion of the left base, however, revealed dullness instead of tympany, with diminished breath sounds. In the cardiovascular system the brachial arterics were soft, straight and smooth. The radials were equal, full, compressible and regular. Blood pressure on both arms was 108/70. The apex-beat was found in the fifth interspace, $9\frac{1}{2}$ cm. from the midsternal line. No increased dullness at the base or to the right of the sternum. The heart sounds were normal. No adventitious sounds were heard.

Neurological examination was negative, except that the patella and Achilles reflexes were exaggerated but equal on both sides. The rectal examination revealed a relaxed sphincter, no hemorrhoids were seen. The prostate was smooth and no apparent enlargement was found.

Laboratory Evidence. Urine examination (twenty-four-hour specimen, 35 ounces). Amber and clear; specific gravity, 1026; acidity, 52; albumin, sugar and ketones, negative; indican, a trace. On microscopical examination a few pus cells and epithelial cells were seen. Lumbar puncture: The spinal fluid was clear and not under increased pressure. Cell count, 3; sugar, slight reduction; globulin, negative; Wassermann test, negative.

Blood Examination. Hemoglobin, 110 (Dare); erythrocytes, 5,030,000; color index, 1; leukocytes, 7060; neutrophils, 54 per cent; eosinophils, 1 per cent; small lymphocytes, 43 per cent; large lymphocytes, 2 per cent. The Wassermann test on the blood serum was negative. Blood chemistry was normal.

Gastric Analysis. Examination of the fasting and test-meal was normal. More details relative to the blood chemistry findings and gastric analysis will be furnished by the writer if desired.

Roentgen-ray Evidence. By fluoroscopic examination of the chest the diaphragm on the left side was seen to move upward with inspiration and downward with expiration. The smooth curved line of the diaphragm was seen to occupy a higher level on the left side than on the right. Barium series revealed a high position

of the cardiac end of the stomach within the chest, also a high fluid level in the stomach was seen. The splenic flexure was found to extend well up into the chest both in the twenty-four-hour observation and the barium enema. The roentgenographical conclusions were eventration of the left diaphragm, high position of the cardiac end of the stomach, displacement of splenic flexure within the chest, paradoxical respiration.

Discussion. In recent years the study of the diaphragm has aroused considerable interest, because it is being constantly appreciated that the diaphragm in its relation to thoracic and abdominal diseases plays a very important part.

Eventration and hernia of the diaphragm were formerly considered to be of purely pathological interest, but since the use of the roentgen-ray in diagnosis there has been a decided increase in the number of these cases reported. Statistics of the last five years, in comparison with those of the last fifty years, will illustrate forcibly this point. However, it is well to remember that these conditions were recognized many years prior to the use of the roentgen-ray for diagnosis.

Historical. The credit is given to Jean Louis Petit, a brilliant French surgeon, for having reported the first case of eventration of the diaphragm. This is mentioned as occurring in 1790, but could not be true because Petit died in 1750. Morrison, of England, rightly calls attention to this fact. He accounts for the error by the statement that the third edition of Petit's writings appeared in 1790. Petit had previously seen at autopsy a case of hernia of the diaphragm. It was found that the stomach, colon and part of the omentum had passed through a defect in the dorsal portion of the diaphragm. There was no hernial sac. Later he observed another case in which there was found at postmortem a small gourd, or tumor, which occupied the left chest. It consisted of stomach and colon enclosed in a hernial sac, and was covered by peritoneum, diaphragm and pleura. He considered the condition to be of congenital origin, and clearly a different one from that which he had observed in relation to the hernia. He, therefore, called the condition "eventratio diaphragmatica."

However, Cruveilhier, in 1849, was the first to describe accurately the condition. Confusion has arisen since then because various writers have used different terms, such as high diaphragm, relaxed diaphragm, insufficiency of the diaphragm, to designate this condition. None of these terms, including eventration, accurately expresses the condition present, but eventration expresses it as well as any. Cruveilhier used the term eventration to designate a high diaphragm, with displacement of the organs of the abdomen into the chest, the walls of the diaphragm thinned, but intact, and with no defect in its continuity. This finding differentiates eventration from hernia of the diaphragm in which a defect or slit in

the diaphragm occurs. Unfortunately this pathological differentiation is not fully recognized, and a study of the literature impresses one with the fact that many writers use the term eventration when they actually have a case of hernia and *vice versa*.

Eppinger, in 1911, compared the relative frequency of eventration and hernia as follows:

	Right side.	Left side.
Hernia vera	21	53
Hernia spuria	34	527
Eventration	2	15

The total cases of eventration were 17, and the total cases of hernia were 635. The ratio of eventration to hernia was 1 to 37.

In 1916 Bayne-Jones described a case of eventration of the right side. He stated that a number of reported cases of eventration had increased to 45, with a corresponding increase in the number of cases of hernia.

Korns, in 1921, expressed considerable doubt as to the accuracy of some of the reported cases of eventration of the diaphragm, and showed by a critical analysis of the reported cases that some were not cases of eventration. He, therefore, summarized the condition of eventration as follows:

Cases in which diagnosis is regarded as proved: Left, 18; right, 4. Cases in which diagnosis was not proved, but regarded as reasonably certain: Left, 41; right, 2. Total left side, 59; total right side, 6. This makes a total of 65.

Since that time there have been reported many additional cases (Funk and Manges, Hurst, Steenhuis, Schaap, Louste, Fatou, Clouston, Stowell, Jewett, Beck, Jaffin and Honeij, Morrison, Muggia, Allan, Withington and Walton).

There are many other cases reported where the terms hernia and eventration were used together and where it was difficult to decide whether the cases reported were those of eventration according to the present conception of the term.

Pathological Anatomy. The pathology of the diaphragm has been studied at autopsy and at operation. In all of the cases of eventration it has been found that the walls of the diaphragm were thin, for example in 1784 Pyl reported a thin membranous sac. This was similar to the findings of Petit, and Meekel, in 1819, made a similar observation. Thoma, in 1882, noted the presence of some fibrous tissue scattered through the diaphragm on the affected side. In Benda's case there was found a lipomatous pseudohypertrophy of the diaphragm, and Motzfeltz reported a case associated with atrophy and fatty changes of the diaphragm.

Hypoplasia of the lung and also malformation of the lung have been frequently found associated with eventration. Other associated lesions observed are as follows: Dextrocardia, dilatation of the colon (called Hirschsprung's disease), dilatation of the stomach

and malformation of the mesentery. Hernias, particularly, have been found. Recently an interesting case of familial hernia was reported by Schreiber. The patient's father suffered from diaphragmatic hernia. She, herself, following the birth of a child, was supposed to have developed an eventration. All of her four children had some form of hernia.

It may be well to call attention to the observations concerning the outward appearance of the chest in cases of eventration of the diaphragm. It has been observed that there was no disturbance in the symmetry of both sides of the chest, even in those cases where malformation and hypoplasia of the lung was observed. This is apparently in accordance with the observations made by Ellis in 1917. He reported an interesting case of a young man, aged twenty years, in whom at autopsy there was found a complete absence of the left lung. There was no change in the outward contour of the chest. He found there were reported in the literature 18 cases, and while most of the cases were in infancy, or had been found in the fetuses, still the condition was not incompatible with adult life. One case at twenty years of age was reported, 2 cases at twenty-four years and 1 elderly patient at sixty-five years of age.

In this condition the opposite lung hypertrophies, and the other side is usually filled with fluid. This finding of symmetry of the chest, associated with absence, or malformation of the lung, is considered to be in favor of congenital origin of eventration, since no change in the contour of a chest has been observed in cases of eventration of the diaphragm.

Other criteria advanced by Thoma in favor of the congenital origin are:

1. The relative frequency of the involvement of the left side of the diaphragm. Attention is called to the embryonic development of the diaphragm. The right side in its development is protected by the liver, whereas the left side is in contact with many organs and is the last to close, and therefore there is the possibility of improper development there.

2. The frequent finding of eventration in the fetus and the newborn.

3. The association of other congenital anomalies.

4. The absence of symptoms over a long period of time.

Thoma felt that the faulty development of the lung allowed the diaphragm and the abdominal viscera to ascend in the thorax.

Doering claimed the condition was primarily a deficiency in the musculature of the diaphragm. Hoffman considered the condition an acquired one and suggested the hypothesis that the chronic dilatation of the stomach, by continued pressure upon the diaphragm, disturbed the blood supply of the diaphragm so as to favor the relaxation of it. This, however, has not been generally accepted.

Traction upon the upper surface of the diaphragm by adhesions has been advanced as a possible cause, but if this were so one should find retraction and diminished size of the chest.

Disease of the nerve has been considered to be responsible for the acquired type. Instances of high diaphragm associated with peripheral neuritis from diphtheria and other toxic states have been seen. A high diaphragm has been observed in poliomyelitis, also with progressive muscular atrophy, but it is clearly evident in these cases that the history will enable one to appreciate the cause.

Morrison, of England, recently reported 9 cases wherein the nerve was found to be secondarily involved with some disease within the chest, and in which a high diaphragm was found by means of the roentgen-ray. The right phrenic nerve was involved in 2 cases, and the left one in 7 cases. Three cases were secondary to carcinoma, 3 secondary to pulmonary tuberculosis, 1 associated with aneurysm and a new growth was found within the chest in the other 2 cases. It is interesting to note in an analysis of these cases that the age of the patient varies from forty-five to fifty-nine years. Autopsy on 2 of the cases revealed the phrenic nerve involved, in both cases with some degeneration of the muscle fibers of the diaphragm, although not to the extent that one would expect, and therefore Morrison suggests the possibility of an axillary innervation of the diaphragm.

Injury during birth has been considered as a possible cause of a high diaphragm. Weigert recently reported a case where trauma occurred during delivery. It was found by roentgen-ray that the diaphragm was high in the chest on the affected side, and after two months it occupied a normal position. Kofferoth made a similar observation relative to the diaphragm and observed paradoxical breathing in a case where forceps were used in delivery.

Therefore the weight of evidence at the present time is such as to favor:

1. Congenital origin.
2. Possibility of primary muscular defect.
3. Possibility of a nerve injury during birth.

Symptomatology. In certain cases of eventration of the diaphragm which were found at autopsy there were no symptoms associated with the condition during life. In other cases the symptoms found may be divided into two groups:

1. Thoracic group.
2. Abdominal group.

With reference to the thoracic group, the chief subjective symptom was dyspnea. In some cases it was present from childhood. Associated with dyspnea in some cases there were recurrent attacks of asthma associated with wheezing, occurring especially after meals. In Petit's case asthma was the chief complaint. Severe

cough has been a prominent symptom, with the expectoration of large quantities of sputa suggestive of bronchiectasis. In other cases severe pain in the chest simulating pleurisy is a prominent symptom. Associated with the pleurisy at times there has been the suggestion of effusion within the pleural cavity, so that a paracentesis was attempted with negative results. Sailer and Rhein reported such an experience. Cyanosis of a severe degree has been observed, and it was especially pronounced in the case of a child while in the prone position and disappeared when in the erect position. Exhaustion and fatigue are associated symptoms.

With the abdominal group, the chief complaint was referable to the gastrointestinal tract with some form of indigestion. The most prominent complaint was the feeling of pressure in the epigastrium and lower chest, associated with marked belching of gas. In other instances severe pain in the abdomen has been the chief complaint. At times the pain has been very acute and so severe as to suggest an acute appendix or an acute obstruction. This may possibly be due to the kinking of the gut, because of its peculiar relationship to the chest. Such an experience has been encountered with a dilated colon, that is, Hirschsprung's disease, associated with eventration of the diaphragm. It is not surprising that obstructive symptoms occur when one takes into account the peculiar appearance of the stomach and its relation to the chest, as has been demonstrated by means of the roentgen-ray.

There is a form of stomach observed in this condition called the spill and cup stomach, best seen in the oblique position in which the pyloric end of the stomach occupies a higher position within the chest than the cardiac end. It can be readily appreciated that if such a condition existed there would be a change in the anatomical relationship of the duodenum and the mesentery.

The possibility of eventration of the diaphragm as a cause of pain in the abdomen in children, due to some disturbance of the anatomical structure of the intestine, should be kept in mind. The pain in certain cases has been severe enough to suggest cholelithiasis.

In addition to the symptoms referable to the chest or abdomen, there is another group of symptoms related to the disturbance of the central nervous system in which there is present melancholia, inability to concentrate, tendency to mental fatigue and evidence of increased nervous excitability which might indicate a possible inferior development of the central nervous system.

Diagnosis. The following procedures have been used in the diagnosis of eventration of the diaphragm:

1. Schlippe's method of measuring the intragastric pressure during the different phases of respiration. It was by the use of this method that Hildebrand and Hess correctly diagnosed a case. However, it is well to call attention to the fact that there are

many conditions which influence the pressure. Minkowski reported positive findings in intragastric pressure when the breathing was of the costal type and in other instances when the breathing was of the abdominal type. The method is a complicated one, and for this reason, as well as the conflicting opinions given as to its value, is impractical.

2. The electrical excitation of the phrenic nerve. Efforts have been made to stimulate the phrenic nerve by means of an electric current and to note the effect of such stimulation upon the diaphragm as seen by the fluoroscope. This method has a distinct disadvantage in that it is difficult to excite in the living individual the phrenic nerve without influencing other viscera.

3. The use of the fluoroscope, and the use of the barium meal. In the majority of cases it is by this procedure that the diagnosis has been made. Certain criteria, when seen by means of the fluoroscope, have been considered diagnostic of eventration of the diaphragm. These are related to the observation of the movement of the diaphragm during respiration. It was found that the affected diaphragm moved on inspiration upward instead of downward. This has been called paradoxical breathing. This is not a constant finding; for it has been shown in certain proved cases of eventration that this did not occur, while in cases of hernia it was observed.

It would seem that the presence or absence of adhesions might influence this observation together with the movement of the contents of the mediastinum. In cases of eventration of the diaphragm, as studied by means of the fluoroscope, one can see an arched smooth line occupying a higher level in the chest than normal. This has been considered diagnostic of eventration in contradistinction to an irregular shadow as is observed in hernia. Another observation, which has been considered of value, is the presence of a high fluid level in the stomach occupying an abnormal position within the chest. Through the evidence obtained by means of the barium meal, the relationship to the chest of the stomach, intestine and colon has been observed.

Roentgenographs of the patient taken in different positions will all show the relationship of posture and its influence on the contents of the stomach.

The roentgenographical examination is very important; in fact, the majority of cases have been diagnosed by this means. When a case is discovered by this method it frequently becomes a curiosity. The experience of the celebrated Schneider case in Europe is of interest in this respect. He visited many clinics. Each clinic subjected him to intensive ray studies, with the final result that he suffered from a severe burn.

4. The use of pneumoperitoneum. This procedure has been used to establish the diagnosis of eventration, but the danger associated with it makes it impractical.

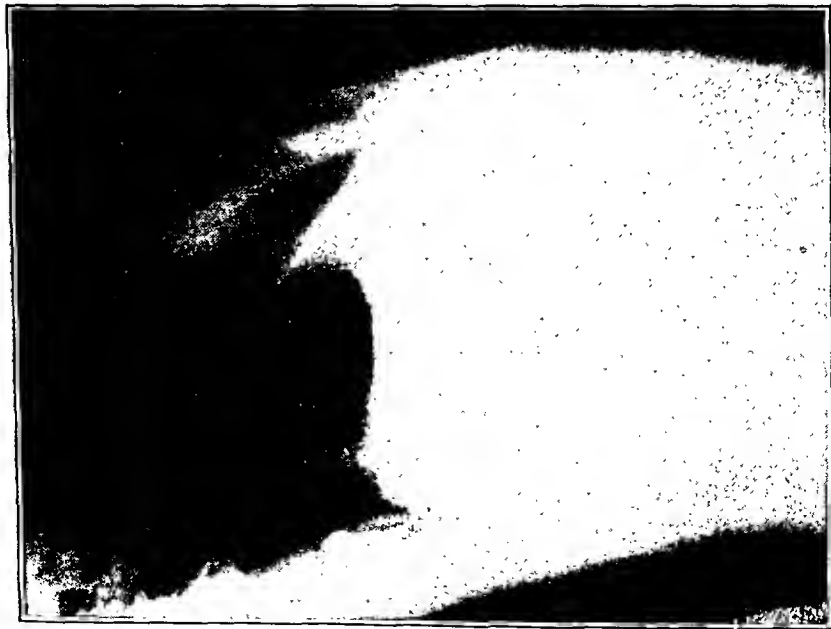


FIG. 1.—Lateral view.

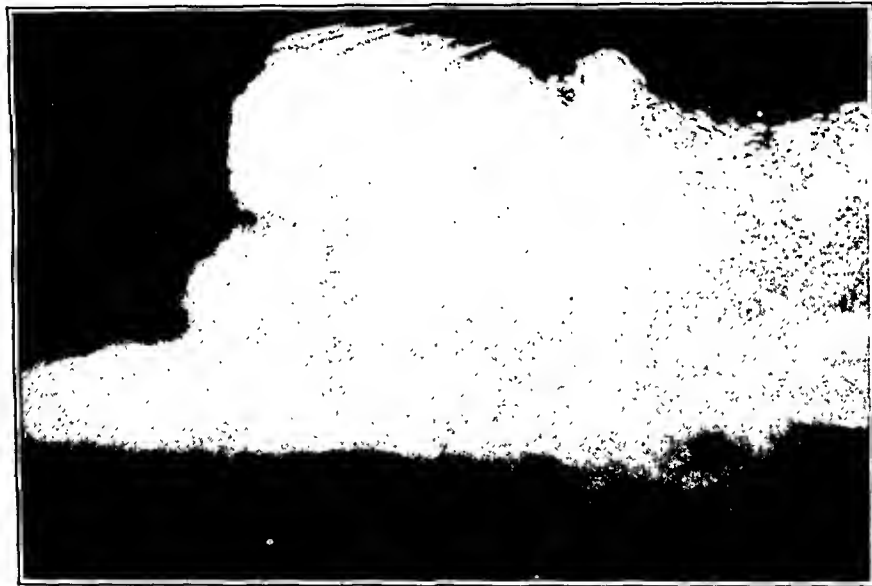


FIG. 2.—Position of barium-filled stomach in chest.

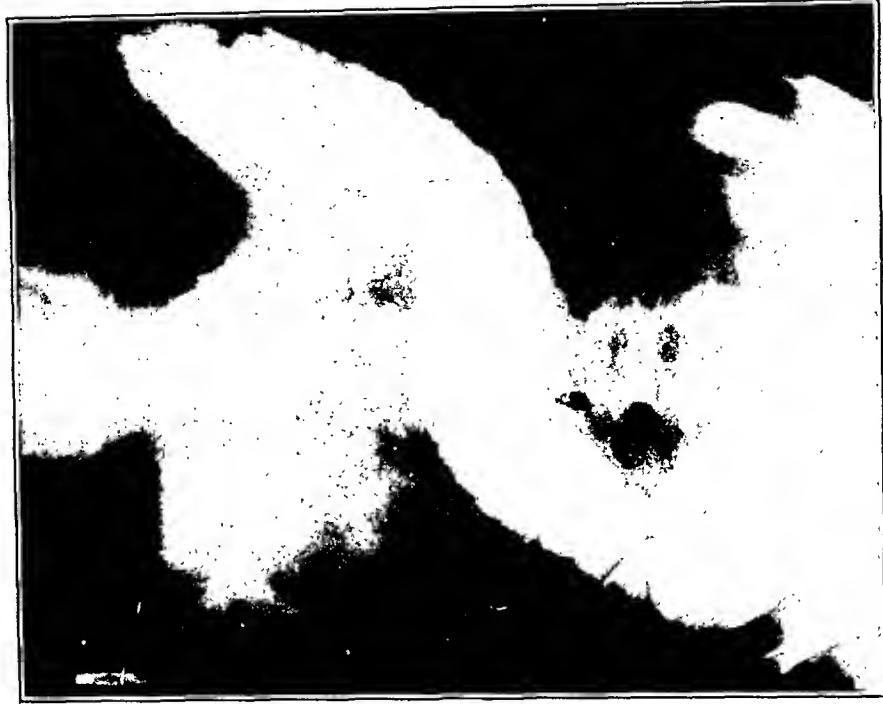


FIG. 3.—Position of barium-filled colon in chest.

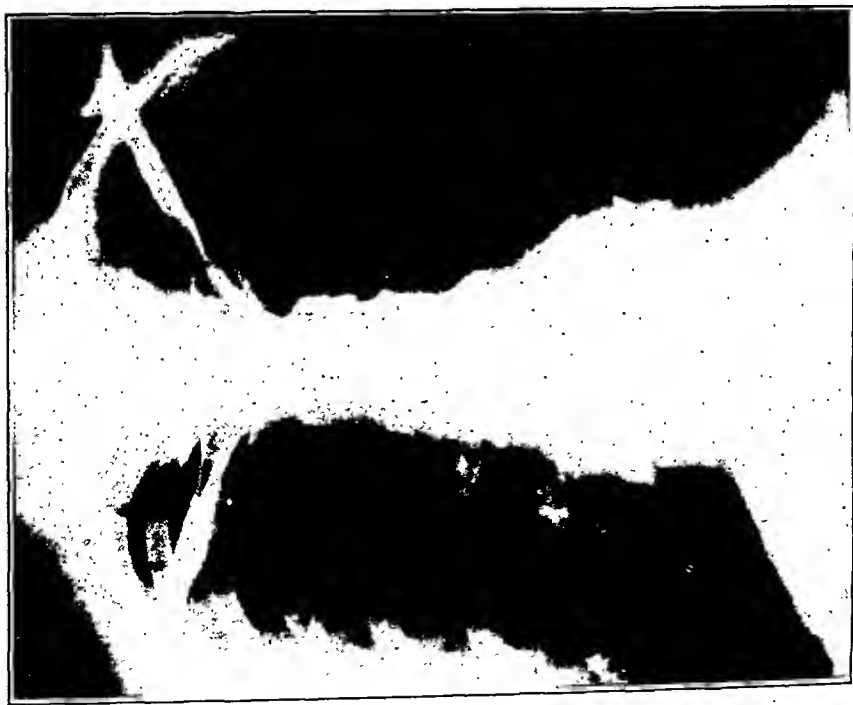


FIG. 4.—Position of diaphragm in forced inspiration.



FIG. 5.—Position of diaphragm in forced expiration.

5. Diagnosis of eventration by means of physical signs. The physical signs of eventration are not entirely characteristic, but nevertheless are extremely valuable. The late Dr. Theodore Janeway made a correct diagnosis of eventration of the right diaphragm from physical examination. By percussion, tympany is usually found at one examination, and later this may be replaced by dulness. This change in the percussion findings is important. The breath sounds are found to be diminished, and at times there is heard splashing and metallic tinkle. These signs vary from day to day, dependent upon the contents of the stomach. The variability of the signs at different examinations should be carefully considered. They may be interpreted as evidence of pneumo-hydrothorax. However, in this condition the history will enable one to differentiate it from eventration, as well as the correlation of these signs and the study of the movements of the costal margin and the change in the subcostal angle.

Hoover has shown by experimental and clinical evidence the importance of careful study of the movements of the costal margins in the differential diagnosis of certain conditions above and below the diaphragm. The use of this method of examination is invaluable. It has proven a most helpful aid to me. Its value is not fully appreciated. This may be due in part to a lack of understanding or misconception as to the physiology of the diaphragm. The value and importance of any method of physical examination depends upon an understanding of the underlying physiology and clinical pathology. Accuracy in technical observation is only obtained by careful and repeated use of the method. Many physicians associate the function of the diaphragm with expansion of the chest and its effect on the vertical diameter of the chest. They are not familiar with the more important function of the diaphragm in its relation to the movements of the costal margin and its effect upon the subcostal angle. This is determined by the plane of activation of the muscle fibers of the diaphragm, the more horizontal the fibers, the greater the degree of activation.

The terms expansion and activation are used by many interchangeably. Failure to appreciate the relationship of the plane of activation of the diaphragm and the action of the intercostal muscles to the movements of the upper and lower costal margins is a common fault. In health this relationship is such as to give to the intercostal muscles the advantage and, therefore, the role of the diaphragm is not fully appreciated, whereas in certain diseased conditions the relationship is so changed as to make evident the role of the diaphragm. In some conditions the plane of activation of the diaphragm is more horizontal and therefore its action increased, whereas in other conditions there is an increase in the curve of the diaphragm, consequently its plane of activation decreased. This observation has been repeatedly proven both

clinically and experimentally. Attention to it will lead to more accurate interpretation of conditions affecting the lower chest and upper abdomen.

When one considers the position of the diaphragm in eventration and its effect on the horizontal plane, and also the position of the diaphragm in hernia, one can use this method of examination as a differential aid.

Funk pointed out its importance in a case which was discovered by the roentgen-ray. He then studied the movements of the costal margins, and stated that the condition could have been recognized if careful attention had been given to these movements. In a more recent communication Korns subscribes to this statement and reports a case to prove the same. In the case reported herewith this observation was extremely valuable and helpful. The importance of this means of examination in the recognition of eventration cannot be overestimated, since most cases are discovered by means of the roentgen-ray. Only a small percentage of patients examined are subjected to roentgenographical examination, and if, therefore, we have a clinical means of examination which will enable us to appreciate this condition I am sure there will be found a greater number of cases than are found at the present time.

Summary. 1. A case of eventration of the diaphragm is reported.

2. The literature as to the various theories of its causation, pathological anatomy, symptomatology and diagnosis is reviewed.

3. Special attention is directed to the possibility of the recognition of this condition by clinical means instead of, as is now done, by means of the roentgen-ray.

4. An important aid is the careful study of the movements of the costal margins, as first described by Hoover.

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EXPERIMENTAL STUDIES ON THE ENTRANCE OF BILE INTO THE DUODENUM.

BY A. WINKELSTEIN, M.D.,

AND

P. W. ASCHNER, M.D., F.A.C.S.,

NEW YORK.

(From the Surgical Laboratories of the College of Physicians and Surgeons, Columbia University.)

In a previous communication,¹ an experimental study of the pressures existing in the various parts of the biliary outflow system was presented. These experiments indicate that the pressure in the common duct is relatively low (60 to 70 mm. of bile) and varies little; that normally the sphincter of Oddi offers to pressure exerted from the common duct side, a resistance of 120 to 130 mm. of saline; that the substances usually present in gastric chyme, when placed on the papilla of Vater, lessen the tonus of the sphincter somewhat, in our experiments one-fifth to one-sixth of the original figure; that 25 per cent magnesium sulphate placed on the papilla acts likewise; that atropin and adrenalin, administered subcutaneously, also reduce the tonus of the sphincter while pilocarpin increases it; that the slight variations in the pressure within the gall bladder are due to tonus changes, the musculature of its wall possessing little, if any, actual contractile power; that reciprocal or contrary innervation or action between sphincter and gall bladder is not demonstrable by the usual methods employed to demonstrate it; and that the intra-abdominal pressure at the end of an inspiration effects a comparatively tremendous increase in the intravesical pressure and almost none in the intraductal pressure.

If these experimental data are applicable in the explanation of normal physiological processes, then, apparently, the variations in the tonus of the sphincter of Oddi and the changes in the intra-abdominal pressure are the two factors of greatest importance in controlling the entrance of bile from the gall bladder and liver into the duodenum. It seems as if the contractile power of the gall bladder wall is of little significance in the emptying act. While these conclusions seem justifiable in view of our studies on the possible pressure variations, they have been supported by observations of what actually takes place both in the operated animals and those fully recovered from operative procedures. These observations will be recorded here.

Spontaneous Activities. (a) *Gall bladder.* A spontaneous gross contraction of the gall bladder with the peritoneal cavity open, was never seen throughout our experiments. It may be added, furthermore, that roentgenological studies on intact animals by means of small silver buttons sewed on the gall bladder,² and by means of roentgen-opaque solutions injected into the gall bladder,³ have proved negative in regard to visible spontaneous contractions.

(b) *Bile flow.* There seems to be a continuous, although varying rate of bile flow into the hepatic ducts. Bile, however, may not enter the duodenum in the fasting, anesthetized animal for periods varying from fifteen minutes to three-quarters of an hour. When it did enter, two types of flow were observed: (1) Slow, irregular, intermittent oozes of a few drops, and (2) somewhat larger, regular, intermittent escapes synchronous with each inspiration.

Stimulation of the Gall Bladder Locally. *Electrical.* A faradic current of varying intensity was used.

EXPERIMENT 1. Dog 3559, male, weighing 8 kilos. Ether anesthesia and median laparotomy. Two cubic centimeters of 0.5 per cent methylene blue solution were injected into the gall bladder. A thin rubber tube was then passed through a small opening on the greater curvature of the stomach into the duodenum. The duodenal content was thus observed for one-half hour. Only light brown bile unstained by the dye was seen. Various points on the surface of the gall bladder, along the cystic duct, and the tissues surrounding the common duct were submitted to faradic stimulation. Neither a perceptible contraction nor a change in size occurred. Dyed bile did not enter the duodenum.

EXPERIMENT 2. Dog 3581, male, weighing $7\frac{1}{2}$ kilos. Ether anesthesia and median laparotomy. The duodenum was incised and a small glass cannula (2 mm. in diameter and 2 cm. long) was inserted through the sphincter of Oddi and tied securely into the common duct at the papilla. The duodenal and abdominal wounds were then closed. The following day laparotomy under ether anesthesia was again performed. The gall bladder, which was found collapsed, was refilled with 12 cc of dog bile and the

faradic current applied as in the previous experiment. A contraction did not result. The cystic duct was ligated and a straight glass manometer was tied into the fundus of the gall bladder. The subsequent application of the faradic current did not produce a rise in the pressure within the gall bladder.

Artificial Distension. Varying degrees of distension of the organ with air and fluid were instituted and the effect on its contractile activities noted.

EXPERIMENT 3. Dog 3257.¹ In this dog, while studying the pressures in the entire duct system, from a few cubic centimeters up to 35 cc of saline were injected into the gall bladder without causing a perceptible contraction.

EXPERIMENT 4. Dog 3394, female, weighing 8 kilos. A collapsed rubber balloon was inserted into the emptied gall bladder and connected with a water manometer. Inflation of the balloon with pressures from 20 to 100 mm. of water did not cause a contraction.

Operative Manipulations. Handling, squeezing, or pinching the organ, grasping with an artery clamp, piercing with a needle, or cutting the wall, did not cause a generalized contraction. Occasionally, a slight, shallow, linear spasm adjoining the traumatized area was seen.

Manual Expression. The emptying of the contents of the gall bladder into the duodenum by manual expression ordinarily requires considerable force. The slightest pressure, however, is sufficient to accomplish this when a duct is cut into or across at any point between the sphincter and the neck of the gall bladder, or when the sphincter is kept patent by a glass cannula as in Experiment 2.

EXPERIMENT 5. Dog 3432, male, weighing 12 kilos. Ether anesthesia and median laparotomy. Methylene blue solution was injected into the gall bladder and the duodenum opened opposite the papilla. Atropin, gr. $\frac{1}{100}$, was administered subcutaneously to relax the sphincter.¹ The abdominal wound was then temporarily closed and antero-posterior pressure applied vigorously for ten minutes. On reopening the abdomen, no dyed bile was found in the duodenum. The abdomen was again closed and the lower thorax and upper abdomen squeezed laterally. The duodenum now contained most of the dyed content of the gall bladder. The common duct was cut across above the sphincter and the slightest pressure on the gall bladder sufficed to expel dyed bile into the free peritoneal cavity.

The Respiratory Squeeze. In the roentgenological studies, already mentioned, of Abramson³ and Winkelstein,² which were made on animals recovered from operative procedures and in good health, a definite craniocaudal squeeze of the gall bladder with each inspiration could be seen. Furthermore, we have also described how this respiratory squeeze effects a large fluctuation in the intravesical

pressure.¹ It is apparent, however, that this increase of pressure may be ineffectual in the emptying process if the sphincter of Oddi remains closed with a sufficient tonus resistance to block the entrance of bile into the duodenum. There is the further possibility that the intra-abdominal pressure may cause a simultaneous pressure increase in the duodenum quantitatively like that in the gall bladder and so prove ineffectual even with the sphincter open. That this is not the case was demonstrated by the following experiment in which the pressure in the duodenum, empty or distended, rose merely 5 to 15 mm. with the respiratory change. Pressure within the gall bladder, it will be recalled, rose to 100 mm. at the end of inspiration.¹

EXPERIMENT 6. Dog 3926, male, weighing 8 kilos. Ether anesthesia and median laparotomy. A straight glass tube was tied into the duodenum at the level of the papilla and connected to an upright water manometer. The abdominal wound was closed tightly about the glass tube and the respiratory fluctuations noted.

	Inspiration.	Expiration.
Duodenal contents	5 to 10 mm.	0
10 cc saline in duodenum	10 mm.	0
20 cc saline in duodenum	10 to 15 mm.	0

The following experiment was next devised to study the effect of respiration when the sphincter is open or relaxed. The results seem so striking as to make this experiment possibly of prime importance in the problem at hand.

EXPERIMENT 7. Same dog as in Experiment 2. After the small glass cannula had been fixed in the common duct partly through the papilla so as to keep the sphincter open, and methylene blue injected into the gall bladder, the duodenal contents were observed with the duodenum and abdominal cavity still open. With each inspiration dyed bile entered the duodenum from the gall bladder. In twenty minutes, the normally distended gall bladder was rendered flaccid. The duodenal and abdominal wounds were then closed and the animal allowed to recover. Eighteen hours later, laparotomy was again performed. The gall bladder was found collapsed and practically empty containing a fraction of 1 cc of dyed bile. The jejunum and ileum contained stained bile.

This experiment shows that the respiratory act squeezes bile out of the gall bladder into the duodenum when the sphincter is open and demonstrates the importance of the sphincter in the normal filling of the gall bladder.

Electrical and Drug Stimulation of the Nerves Innervating the Gall Bladder. *Electrical.* The following experiment is typical of several attempts made to cause a contraction or relaxation of the gall bladder or an expulsion of its contents by means of faradic stimulation. These attempts were invariably attended by negative results.

EXPERIMENT 8. Dog 3359, male, weighing 8 kilos. Ether anesthesia and median laparotomy. One end of a thin, soft, rubber tube was inserted into the duodenum through an opening in the greater curvature of the stomach and the other end led out through a stab wound in the lateral abdominal wall. The abdominal wound was then sewed up tightly. The vagus nerve was exposed in the neck and the animal allowed to come out of the anesthesia. The faradic current was then applied to the uncut nerve and later to its cut end. Dyed bile did not appear in the duodenum. The abdominal cavity was again opened and the electrodes applied to the tissues about the cystic and common ducts and along the lesser curvature of the stomach. Neither a contraction of the gall bladder nor a change in its size was seen and dyed bile did not enter the duodenum.

Drug Stimulation. In the previous experiments on the pressure factors in the biliary duct system,¹ pilocarpin, adrenalin, and atropin, were administered repeatedly in order to affect the involuntary nerves supplying the sphincter of Oddi and the gall bladder. While these drugs caused some pressure changes within the gall bladder these were only in the nature of tonus variations. Actual gross contractions, changes in the size of the organ, or expulsion of its contents were not seen. In the following experiment, performed later, a decrease in the size of the gall bladder occurred after pilocarpin. This had no practical effect since no emptying took place, although the dosage used was very large.

EXPERIMENT 9. Dog 3432, male, weighing 12 kilos. Ether anesthesia and median laparotomy. A thin, rubber tube was inserted into the duodenum through an opening in the greater curvature of the stomach and methylene blue was injected into the gall-bladder. Pilocarpin, $\frac{1}{12}$ gr., was injected intravenously. The stomach and intestines were thrown at once into a severe tonic contraction. The gall-bladder wall tightened generally and the organ decreased one-third in size. Dyed bile, however, did not enter the duodenum (simultaneous contraction of the sphincter of Oddi?). Atropin, $\frac{1}{75}$ gr., was given subcutaneously, and the contractions disappeared at once but dyed bile did not enter the duodenum.

Secretin. In three dogs, an extract of the duodenal mucosa was made in the usual manner and 2 cc were injected intravenously. There was no apparent effect on the motor activities of the gall bladder.

Reflex Stimulation of the Gall Bladder. In the studies on the pressure factors¹ many chemicals were instilled in the opened or closed duodenum over the papilla of Vater. Some of these, notably magnesium sulphate and peptone, relaxed the sphincter of Oddi. None, however, caused a visible contraction or emptying of the gall bladder. Distending or irritating the mucosa of the stomach

and duodenum, stretching the pylorus, pinching and rubbing the mucosa of the duodenum, were likewise without appreciable effect.

It must be borne in mind, however, that these observations were made with the animal under ether anesthesia, the abdominal cavity open, and often with the duodenum and stomach incised. In the belief that the factors of trauma and anesthesia interfere with the normal physiological nerve responses, a different type of experimentation was next employed. These experiments have already been briefly reported,⁴ but will be described here in full.

In general, the experimental procedure consisted in anesthetizing the dog, injecting a dye stuff into the gall bladder, inserting a soft rubber tube into the duodenum through an opening in the greater curvature of the stomach, leading this tube out through a stab wound in the lateral abdominal wall, suturing the laparotomy wound, and allowing the animal to recover. Following the recovery from the anesthesia and the operation, observations on the duodenal contents were made, chiefly on the effect of the injection of warm saline and magnesium sulphate into the duodenum. It was found that the dyestuff could be more readily distinguished in the supernatant fluid when the bile pigments were precipitated by saturated lead acetate or barium sulphate.

EXPERIMENT 10. Dog 3665, male, weighing 14 kilos. Ether anesthesia and median laparotomy. Two cc of 0.5 per cent methylene blue were injected into the gall bladder. A thin, soft, rubber tube was passed through an opening in the anterior stomach wall at a point near the greater curvature, into the duodenum. The stomach end of the tube was led out through a stab wound in the lateral abdominal wall. With the abdomen open, 40 cc of 25 per cent magnesium sulphate were repeatedly injected into the duodenum and aspirated. Only light brown bile unstained by the dye was obtained. The laparotomy wound was then closed and the animal allowed to recover.

Observations. Nineteen hours postoperative; before and after the instillation of warm saline and magnesium sulphate into the duodenum, only yellow bile was obtained.

Twenty-four hours postoperative; thirty-five minutes after bread and water was eaten by the dog, 3 cc of dark green dyed bile were aspirated.

Forty-six hours postoperative; before and after warm saline, pale greenish-yellow bile was aspirated. After 40 cc of 25 per cent magnesium sulphate, however, bile, stained deeply green, was recovered.

Forty-nine hours postoperative; after saline, magnesium sulphate, and food, only light yellow-brown bile was found in the duodenum.

Subsequent Observations. During the next four days, the effect of saline, magnesium sulphate, peptone, and food, was observed. Only bile varying from yellow to brown without dye was seen. On

the seventh postoperative day, the abdomen was opened under anesthesia. The gall bladder was normally distended with 10 cc of brown bile. The tonus of the sphincter of Oddi was preserved; it was found to measure 115 mm. of saline (average tonus).

Discussion. Apparently, after magnesium sulphate and food and not after warm saline, bile from the gall bladder entered the duodenum. It seems probable also that the dyed specimen of bile left the gall-bladder in forty-six to forty-nine hours.

EXPERIMENT 11. Dog 3740, male, weighing 7 kilos. The procedure was the same as that in the previous experiment.

Observations. Fifteen minute postoperative; 2 cc of brown bile were aspirated from the duodenum.

Twenty-two hours postoperative; before and after warm saline, only yellow-brown bile was recovered. Following the instillation of magnesium sulphate, bile, moderately green-stained, was aspirated.

Forty-six hours and the next three days postoperative; after saline, magnesium sulphate, and food, yellow-brown bile was found in the duodenum.

Subsequent Observations. Under anesthesia, the dog's abdomen was opened six days after the operation. The gall bladder was found normally distended with 10 cc of moderately dark brown bile.

Discussion. After magnesium sulphate and not after saline, bile from the gall bladder entered the duodenum. The gall bladder was probably emptied of the dyed bile in twenty-two to forty-six hours.

EXPERIMENT 12. Dog 3760, male, weighing 14 kilos. Procedure as in the previous experiment. 100 mg. of phenoltetrachlorphthalein was also injected into the gall bladder.

Observations. Fifteen minutes postoperatively; 3 cc of brown bile without dye were aspirated.

Twenty-one hours postoperatively; before and after saline unstained bile was found in the duodenum. After magnesium sulphate, green-dyed bile containing phenoltetrachlorphthalein was aspirated.

Twenty-five hours postoperative; one-half hour after food, only brown bile without dye was recovered.

Subsequent Observations. For six days, after saline, magnesium sulphate, and food, yellow to brown bile was obtained. On the seventh day, 50 mg. of indigo carmine was injected intramuscularly. Twenty-four hours later, after magnesium sulphate and not after saline, dyed bile appeared in the duodenum. Under anesthesia, the abdomen was then opened and the gall bladder was found to contain 7 cc of bile stained a deep green by the dye.

Discussion. It does not seem necessary to make any other comment than to state that the gall bladder was probably emptied of the dyed bile in twenty-one to twenty-five hours.

EXPERIMENT 13. Dog 3916, male, weighing 8 kilos. The procedure was the same as in the previous experiment except that 5 cc of Neo silvol, stained by indigo earmine, was injected into the gall bladder after the withdrawal of 5 cc of bile.

Observations. In brief, it was found that after magnesium sulphate and not after saline, dyed bile entered the duodenum and that the dyed bile had left the gall bladder in forty-eight hours.

Summary. A full discussion of these experiments and their possible significance will be reserved for a future publication. The experimental observations may, however, be summarized briefly here.

1. No evidence was found of spontaneous contractions of the gall bladder in the dog, either under anesthesia or when fully recovered.

2. It is possible to empty the gall bladder by manual expression after the sphincter of Oddi is relaxed, with the peritoneal cavity open or closed.

3. The respiratory squeeze, that is, the increase in intra-abdominal pressure at the end of inspiration, also effects an expulsion of bile into the duodenum from the gall bladder when the sphincter of Oddi is relaxed.

4. Direct or reflex stimulation of the gall bladder, whether it be by faradization, drugs, hormones, chemicals, or mechanical means, does not cause a contraction of the gall bladder, or an appreciable change in size, or any emptying, in the experimental animal under anesthesia.

5. In an animal, however, which has fully recovered from the operative procedures, following the instillation of 25 per cent magnesium sulphate or the passage of gastric chyme into the duodenum, and not after normal saline, there is an entrance of bile from the gall bladder into the duodenum.

Whether the more normal physiological conditions in the last instance permit of gall bladder contractions sufficiently strong to expel bile seems extremely doubtful from our experimental observations. It is more probable that certain agents, viz., magnesium sulphate and gastric chyme, relax the sphincter of Oddi and that then, the intra-abdominal pressure at the end of each inspiration expresses some bile from the gall bladder into the duodenum.

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A NEW METHOD FOR STUDYING PURE GASTRIC SECRETION.*

BY A. L. GARBAT,

ASSOCIATE VISITING PHYSICIAN AND BACTERIOLOGIST (LENOX HILL HOSPITAL), NEW YORK CITY.

WE have been accustomed, clinically, to study gastric secretion by means of the various types of test meals. In this way, however, we are dealing with gastric contents which contain not only the gastric juice, but also constituents of the test meal, besides swallowed saliva.

The first accurate observations on pure gastric juice in man were made by Dr. Beaumont in 1833, on a Canadian voyageur who, by the premature discharge of his gun, was left with a permanent gastric fistula. By this method, samples of gastric juice could be secured, but not while the digestive process was actually in progress. To make the collection of such a sample possible, experiments in animals were resorted to. Heidenhain isolated portions of the stomach wall as pouches opening through fistulæ on the abdominal wall. The objection to this procedure was that the secretion in the isolated pouch did not necessarily correspond to that occurring in the main stomach, since the connection of the pouches with the central nervous system was severed. In order to overcome this disadvantage, Pavlow¹ devised the ingenious operation of a miniature stomach which remained connected with the main stomach without severing the nerve connections. Naturally, this procedure is applicable only for experimental purposes in animals. In man, it is only the gastric fistula cases with stenosis of the esophagus, similar to Dr. Beaumont's patient, which offer the pure type of gastric secretion; but such patients are rare, and gastric problems can only be definitely answered by studies upon many subjects². There is no organ in the body, the function of which is more influenced by individual reaction, than the stomach. Gastric juice without food admixture has usually been collected by aspiration of the fasting stomach, but contents thus obtained suffer the disadvantages of having been in the stomach for varying lengths of time, of not being produced during the cycle of digestion, and of being contaminated by swallowed saliva or regurgitated bile.

In the course of the author's studies on duodenal alimentation, the two-tube method^{3, 4} was found very satisfactory for obtaining pure gastric secretion during the act of digestion. The technic is comparatively simple. The patient swallows the duodenal tube (Einhorn type), which is allowed to pass into the duodenum in the usual way. After it is proven definitely in place, another duo-

* (From the Laboratory and Medical Division of the Lenox Hill Hospital, Service of Dr. J. Kaufmann.)

denal tube is then swallowed, but this second one remains in the stomach. When gastric juice is wanted, duodenal alimentation should be started through the duodenal tube, best done by means of the regular Einhorn Duodenal Feeding Outfit. The author has found that in response to the duodenal feeding there is an immediate secretion of gastric juice which can be easily aspirated from the stomach, through the gastric tube.

It is wise to empty the stomach of any contents that it may contain before the duodenal alimentation is started. Then too, one must be certain that the tube in the stomach rests in its most dependent portion, otherwise aspiration will not bring forth all the gastric secretion. At times, it may require the roentgen-ray to see the proper position of the tube. It is often necessary to change the posture of the patient from reclining to sitting, or *vice versa*, or from one side to another.

The gastric secretion starts almost immediately after the injection of the first 20 to 30 cc of fluid into the duodenum, and is most marked during, or right after, the feeding (which should take twenty minutes), but often continues for about thirty minutes to an hour after the duodenal alimentation has been stopped.

We found several important factors which influenced the gastric secretion.

Type of Patient. It was shown⁴ that the amount and character of gastric juice which can be collected in response to duodenal feeding depends upon the type of patient dealt with, and compares very closely to what the gastric secretion would be in that same patient in response to the gastric test meal. Thus, a patient with an achylia gastrica shows no gastric secretion in response to duodenal feeding. A patient with a mild irritative form of gastric disorder offers a moderate amount of gastric secretion—about 100 cc, while patients with a marked irritative form of gastric function, as cases of alimentary hypersecretion, give as much as 280 cc of pure gastric juice in response to a duodenal feeding.

Type of Duodenal Feeding. Most of the experiments were done with duodenal alimentation, consisting of a mixture of 7 ounces of milk, 2 eggs, $\frac{1}{2}$ dram of lactose, 1 square of butter and a pinch of salt.

Different types of feeding were undertaken in the same person to note any possible difference in the response of gastric secretion. The most striking example was seen in a patient with a gastric ulcer and alimentary hypersecretion; comparative experiments, after individual feedings with 8 ounces of saline, 8 ounces of beef broth, 8 ounces of milk-egg mixture, and 8 ounces of thick strained oatmeal gruel, showed the least amounts of gastric secretion, that is, 100 cc and 138 cc following the saline and the broth respectively; the greatest amount (377 cc) was stimulated by the 8 ounces of gruel, while the milk-egg mixture gave 286 cc.

CHART.—GASTRIC SECRETION AFTER DUODENAL FEEDING WITH VARIOUS SUBSTANCES.

Time of aspiration after starting duodenal feeding.	Normal saline (8 oz.)			Beef broth (8 oz.)			Milk-egg mixture† (8 oz.)			Thick oatmeal gruel (8 oz.)		
	Quantity of aspirated gastric secretion.	Free* HCl.	Total* acid.	Quantity of aspirated gastric secretion.	Free HCl.	Total acid.	Quantity of aspirated gastric secretion.	Free HCl.	Total acid.	Quantity of aspirated gastric secretion.	Free HCl.	Total acid.
15 minutes	70 cc	22	38	90 cc	44	53	98 cc	51	69	175 cc	54	62
30 "	30 cc	36	44	30 cc	52	62	80 cc	51	64	110 cc	54	62
45 "	Duodenum empty											
	18 cc	52	60	50 cc	48	68	35 cc	52	62
60 "	Duodenum empty	38 cc	54	68	25 cc	54	66
75 "	Duodenum empty	60	70	25 cc	74	78
90 "	15 cc	4	20	Duodenum empty	32	20
							5 cc			7 cc		

* As determined by titration with tenth-normal NaOH per 100 cc.

† Consists of 7 ounces of milk, 2 eggs, $\frac{1}{3}$ dram of lactose, 1 square of butter, pinch of salt.

From repeated experiments with similar results, this difference was explained by the finding that the longer the feeding remained in the duodenum, as evidenced by aspiration, the longer did the gastric secretion continue. In all the tests, as soon as the duodenum became empty, the gastric secretion practically ceased. The saline and broth passed out of the duodenum most quickly, while the gruel stayed longer than the milk-egg mixture.

Discussion. The excitation of gastric secretion by application of food substances to the duodenal mucosa, had not heretofore been demonstrated sufficiently conclusively in man.

In animals, this was first shown by Pavlov and his coworkers.¹ Gross⁶ employed a duodenal and a gastric fistula in animals, and observed that when meat extract was put into the intestines, a stimulation of the gastric glands resulted. Similar animal experiments with different food agents are reported by Zeligy,⁷ Lonnquist,⁸ Chittenden, Mendel and Jackson,⁹ Edkins and Tweedy,¹⁰ and Tomaszewski.¹¹

The most recent and very detailed studies along these lines were published by Ivy and McIlvain.¹² Their experiments were made on dogs, with a Pavlov pouch in the stomach, and a Thiry's fistula in the duodenum and jejunum. In this way, there was produced a loop of duodenum and jejunum fifteen to eighteen inches long, to which substances could be continuously applied, and the resulting secretion in the Pavlov pouch noted. A great number of active and constant excitants were demonstrated. These workers also made experiments upon two men in whom twentieth-normal HCl was injected into the duodenum through a duodenal tube, after which gastric secretion resulted.

Regarding the mechanism concerned in the excitation of gastric secretion by way of the upper intestines, several factors may play a role. While it seemed certain to the writer that secretion continued as long as food substances remained in the duodenum, this was not due to a simple distention of the duodenal loop. Ivy and McIlvain¹² found that when the loop was distended with from 50 to 75 cc of air or water, no stimulation of gastric secretion occurred. Pavlov suggested that it may be due to a local secretory reflex from the intestinal mucosa to the gastric mucosa. On the other hand, it may be a long reflex to the cerebral centers, and a centrifugal response with either a secretory or vasomotor effect. The possible stimulation by secretin produced in the intestinal mucosa must also be considered, although the almost immediate appearance of the gastric secretion after the duodenal feeding, as is regularly noticed in the human being, without a latent period, speaks somewhat against the hormone element. The possibility of a psychic factor in influencing the results is, of course, always to be kept in mind. Definite explanation must therefore be withheld.

Summary. 1. The two-tube system, with the physiological phenomenon that gastric secretion takes place in response to duodenal feeding, offers a new method whereby we can collect large quantities of pure gastric juice, as soon as it is secreted, during the act of digestion, and without admixture of any test meals.

2. The instigated gastric secretion differs with various articles of food, and continues as long as the particular food contents remain in the duodenum.

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THE NEOPLASTIC NATURE OF THE LEUKEMIC PROCESS.

By A. PINEY, M.D., M.R.C.P.,

INSTITUTE OF PATHOLOGY, CHARING CROSS HOSPITAL MEDICAL SCHOOL, LONDON.

THE conception of the leukemic process as a truly neoplastic one is not new, and has been supported by a number of writers, *e.g.* Banti,² Babes,¹ Ribbert,¹⁴ Benda,³ Mallory¹¹ and others, but has not obtained wide acceptance. Sternberg has attempted to show that the large-celled form of lymphatic leukemia is a neoplastic process (leukosarcomatosis), but the other forms of leukemia are not explained on his hypothesis. An infiltrative mode of growth is insufficient evidence of the neoplastic nature of a disease, and this alone is sufficient to invalidate the conception of Banti. Lenaz¹⁰ has attempted to form a definition of neoplasia, and comes to the conclusion that all forms of leukemia are neoplastic and carefully excludes all those hematological reactions of similar character which have no histological relationship with the leukemias. This is doubtless a proper distinction to make, but the very fact that "leukemoid" reactions do occur independently of leukemia would seem to indicate that a similar impetus of some kind is at work. If leukemia can properly be regarded as neoplastic it is essential that a definite tumor should be demonstrated, even if the blood picture itself and the infiltrations of the tissues cannot be regarded as being of metastatic nature.

It is not uncommon to regard all forms of leukemia as of hyperplastic nature, but the absence of a clear conception of the nature of such a process is a bar to its acceptance. If the term hyperplasia be confined to those processes in which an increase of normal cells in normal arrangement is the essential feature it will be obvious that leukemia is not of this nature. An inflammatory reaction differs essentially from a neoplastic one, in that many phases of cell activity and structure are present at the same time, while in a tumor only one type of cell proliferates in an atypical manner, that is, there are a number of phases in an inflammatory focus but only one in a neoplastic one. The application of these conceptions to the leukemic process should present little difficulty, so long as the changes in the hematopoietic organs and not the characters of of the blood picture be regarded as the essential features.

If the lymphatic type first be considered (lymphadenosis) in its chronic form, it is to be noticed that two types of blood picture may occur; the two types (shown below) may occur in the same case at different times, but when the first type has disappeared it never returns.

TABLE I.—TYPES OF DIFFERENTIAL COUNT IN CHRONIC LYMPHATIC LEUKEMIAS.

	Type I, Per cent.	Type II, Per cent.
Polymorphonuclears	22	7.9
Eosinophiles	2	0.15
Basophiles	0	0.2
Monocytes	4	1.85
Lymphocytes	72	87.4
Metamyelocytes	0	0.1
Myelocytes	0	0.25
Myeloblasts	0	1.8
Lymphoblasts	0	0.2
Plasma cells	0	0.15

It will be noted that the essential difference between the two types is the presence of immature cells of the myeloid series in the second type, in which also nucleated red cells are much more common.

Acute lymphadenoses usually are of the second type, and a case with no immature myeloid cells is a great rarity. Naegeli¹² regards the presence of such cells simply as a result of irritation, but does not state the nature of the stimulus. Fig. 1 shows the appearances of a section of bone marrow from a case of chronic lymphadenosis, which had reached the second stage. It will be seen that a mass of lymphocytes is surrounded by hyperplastic marrow tissue, which is only incompletely separated from the lymphocytic mass. Fig. 2 shows a section from the marrow of a case of carcinoma of the breast with metastases in the bones; here there is a mass of carcinoma cells surrounded by a zone of hyperplastic myeloid tissue

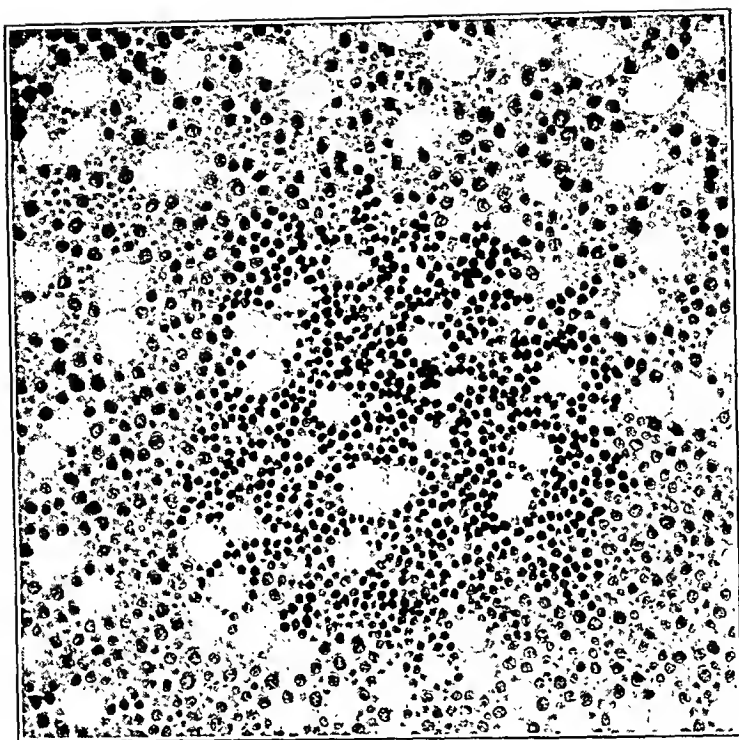


FIG. 1.—Section of marrow from cases of chronic lymphadenosis. The section shows a mass of small lymphocytes in the center and this is surrounded by myeloid tissue in a state of well-marked hyperplasia.

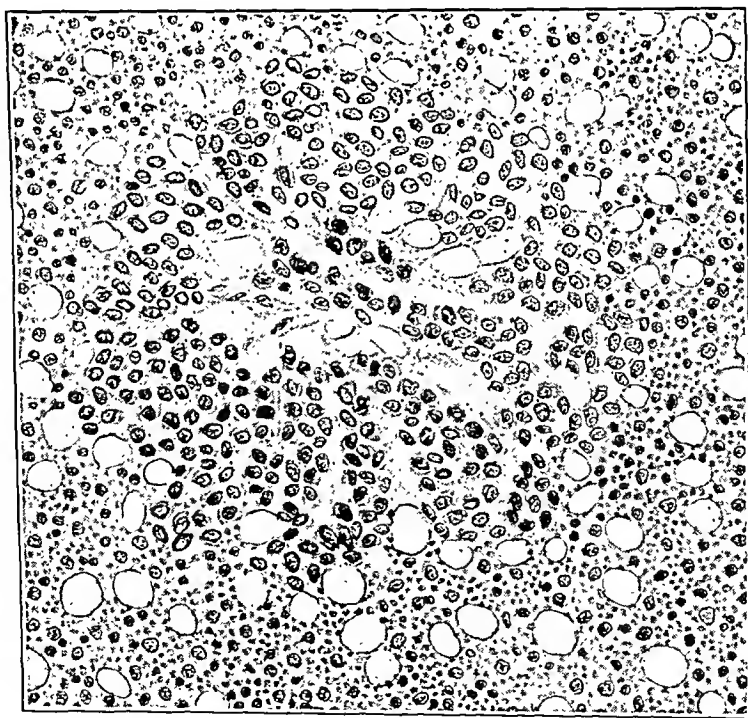


FIG. 2.—Section of marrow from case of metastatic carcinoma of bone. The central part of the field shows a mass of epithelial cells which are surrounded by intensely hyperplastic marrow tissue. The resemblance to Fig. 1 is very striking and the sole difference is found in the nature of the cells composing the central mass.

of a character identical with that seen in Fig. 1. The blood in this case showed 12.75 per cent of immature myeloid cells, that is, a percentage even higher than that found in the second type of lymphadenosis recorded above. The hematological distinction between the two conditions lies in the much greater total number of leukocytes and much higher percentage of lymphocytes in leukemia than in metastatic cancer of the marrow, but the myeloid picture does not differ appreciably in the two diseases. The fact that leukemic proliferations of marrow differ in their arrangement from normal marrow can be seen quite easily in sections and the leukemic process differs also from the ordinary hyperplasia associated with severe leukocytosis. In lymphadenosis these differences are naturally more marked than in myelosis, as here the former process causes growth of a foreign tissue in the marrow which displaces and destroys the myeloid tissue—this would appear to be a true neoplasm.

The blood picture is certainly more difficult to interpret than is the histological picture in the hematopoietic organs, as here there are two distinct features, namely, the emigration of immature leukocytes as the result of the simple hyperplasia of the marrow around the lymphocytic foci and the flooding of the circulation with lymphocytes from the tumor-like masses.

The first appearance of immature myeloid cells in the blood seems to correspond to the time when focal points of tenderness of bones can first be noted clinically, and such points of tenderness always correspond to microscopical areas of lymphocytic infiltration. It must be recalled also that Naegeli¹² has recorded a case of typical lymphatic leukemia in which spontaneous fracture of a rib occurred.

The tumor-like foci in cases of myelosis are usually composed only of myeloblasts, which form groups of 20 to 200 cells in which no signs of development into premyelocytes can be found, although the surrounding tissue shows this mode of maturation in great quantity, that is, these are monophasic foci. Rarely the foci in myelosis are composed of myelocytes and even less commonly of premyelocytes, and in these cases the blood picture at the end of life is predominately myelocytic or premyelocytic instead of myeloblastic, as is usually the case. These facts appear to show conclusively that cells from the monophasic foci can emigrate into the blood stream and, if this is so, and if they are tumor cells, it should be possible to recognize them in the blood before the end of the disease. If the cells in films from cases of myelosis be carefully examined it is always possible to find that the percentage of atypical myeloblasts (premyelocytes or myelocytes according to the type of case) increase as the disease progresses until, toward the end, few typical cells of the group can be found in the blood. It is equally important to note that such abnormal forms are not

found in the blood in cases of metastatic tumors of bones. It is inconceivable that the abnormality of some of the blood cells depends upon injury by an unknown agent, as the rate of reproduction is so much greater than normal—an occurrence which is extremely improbable in injured cells. The general appearance of the marrow is that of an intensely active organ, such as could scarcely be the result of toxic injury.

The length of the clinical history of many cases of leukemia can be employed as an objection to the neoplastic conception only if the disease be regarded as a malignant neoplasm, which would seem to be a necessary conclusion only in relation to the acute forms of the type which were excluded from the neoplastic hypothesis by Sternberg.

In brief, the conception put forward in this paper is that of a neoplastic process, which, like other tumors, is more rapid in its course when composed of immature cells and which gives rise to a striking blood picture by two means, namely, irritation of the bone marrow and emigration of the tumor cells themselves in progressively greater numbers as the disease progresses and the amount of functional marrow decreases.

The appearances of the marrow, and of the blood (Piney¹³) show that the emigration of immature cells cannot be attributed to a depletion of the tissue and consequent paucity in mature forms.

It is necessary to mention briefly some of the arguments in favor of the other views of the nature of the leukemic process. An infective origin of, at least, some forms of the disease has frequently been very strongly supported, for example, Sternberg¹⁴ has contended that the acute myeloblastic form is not a special malady, but is a peculiar reaction to a variety of infections. He claims that it is possible to produce an intense myelocytosis in the blood and well-marked myeloid change in the tissues by injection of streptococci, but he appears to ignore the essential feature of leukemia, namely, the focal arrangement of masses in the marrow.

Von Hansemann⁷ propounded a most attractive view, which can at present be little more than a working hypothesis: He suggests that the changes in the tissues in leukemia are so unlike true tumors that no other possibility than infection remains to be considered, and he suggests that leukemia may be a condition secondary to an infection. Herz^{8, 9} has taken up a similar attitude, and pointed out that lymphomata in the liver are common in typhoid fever, and suggests that such tissue formations may be the morphological basis of a predisposition to leukemia. The experimental work of Ellermann^{4, 5, 6} on the leukosis of fowls is the most striking evidence in favor of the infective theory, but the histological changes found in these animals differ from those found in human leukemia in that they appear to be purely hyperplastic and metaplastic.

The appearances of the neutrophile polymorphonuclear leukocytes and in fact of the neutrophile cells as a whole in leukemia is very striking, because there is a shift to the left of the Arneth index, that is, a decrease in nuclear complexity with even the appearance of quite immature forms, namely, myelocytes, but at the same time there is also an increase in the number of many-lobed polymorphonuclear leukocytes—some with as many as seven lobes in the nucleus. These are not the appearances found in infective diseases. The fact that eosinophile leukocytes may increase at the same time as the neutrophiles is some evidence against the conception of an infection because, as a rule, the eosinophiles fall when the neutrophiles increase in number.

The occurrence of such a condition as myeloblastic leukemia is very difficult to reconcile with an infective origin, as it is now known that the granular cells increase mainly by division of preëxisting granular cells (myelocytes) and not by derivation from the non-granular myeloblast (Ellermann⁶), which appears to fulfill its function in embryonic life. If this fact be admitted it is obvious that the excessive proliferation of myeloblasts cannot be explained by the presence of an additional demand for granular cells, as this should result in an increase of myelocytes.

Ziegler¹⁶ supposed that normally there was a sort of balance between the lymphatic and the myeloid tissues of the body, and he was able to cause myeloid metaplasia by destruction of the Malpighian bodies of the spleen. But the appearance of his specimens was not that of leukemia, and there is certainly no abnormality of lymphatic tissue in the early stage of myelosis.

Naegeli¹² supposes that leukemia is a disturbance of correlation, but presumes that the error is in the balance of the endocrine system. It may be admitted, that in the absence of a nerve supply, the regulation of the hematopoietic organs must be of chemical nature, but this could normally govern only the emigration of mature cells and the size of the functional organ, for example, bone marrow, but in leukemia there is a qualitative as well as a quantitative change which would require some other explanation. If such an endocrine disturbance be supposed to be the cause of leukemia it is an obvious corollary that the malady must affect the whole of the hematopoietic system—this is certainly not the case, as areas of normal blood-forming tissue can always be found, even in advanced cases, that is, not all the lymphatic or myeloid tissue is affected at the same time or to the same extent.

The view of von Hanseemann, that an infective origin must be postulated because no other view will fit all the known phenomena, is thus not correct and, in fact, it might well be supposed that by a similar process of exclusion all conditions other than neoplasia might be excluded.

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HETEROTOPIA OF ADRENAL IN LIVER AND KIDNEY.*

BY CARL VERNON WELLER, M.S., M.D.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN.

(From the Department of Pathology, University of Michigan, Ann Arbor, Michigan.)

IN its varying degrees heterotopia of the adrenal in the liver or kidney appears to be a much more common developmental disturbance than the literature upon the subject would lead one to expect. Four well-marked examples of this condition have appeared in the last 800 autopsies done in the Pathological Laboratory of the University of Michigan. Yet adrenal heterotopia in liver and kidney has been quite generally ignored in the monographical presentations of diseases of the adrenal and in systems of medicine. One of the most recent of these simply says that "One case, at any rate, has been reported in which the right suprarenal was found beneath the fibrous capsule of the kidney," and predicts that the future development of endocrinology may reveal further occurrences of such anomalies.

By definition, from the groups of adrenal-renal heterotopia and adrenal-hepatic heterotopia, forming the subject of this report, there must be excluded the accessory adrenals that may be found upon, in or beneath the capsules of these organs, and likewise there must be excluded the more or less undifferentiated tissues of nephros origin which may be found within the kidney, particularly, some of which come to resemble adrenal cortex. It is fully recognized

* Presented at the meeting of the American Section of the International Association of Medical Museums, Buffalo, April 17, 1924.

that the different types of malposition which may be properly designated heterotopia may be in a sense a major degree of these conditions just excluded, but from every point of view, except the embryological one, they are fundamentally different. In the various types of inclusions and "rests" which we bar from this category by definition, an adrenal is to be found upon the same side. With heterotopia no adrenal other than the one included is to be found upon that side. To these dicta which appear so simple and so fundamentally sound there are at least three reported exceptions. One was briefly described by Grawitz,² another by Radasch,⁷ while the third is a case described by Miloslavich,⁴ in which there was a duplication of one adrenal so that, while there was apparently a true and complete unilateral adrenal-renal heterotopia, another well-formed adrenal was found upon the same side. Exceptions of this nature, involving complete duplication of the adrenal and a heterotopia of one of the resulting pair, must be rare, so that, in general, the presence of a well-formed adrenal in normal relationship is against, but does not entirely rule out, heterotopia of the adrenal on the same side.

The importance of the condition here described is more than an academic one. It is true that it probably will never be recognized except in the operating room and at autopsy, but its correct interpretation is of great importance both to the surgeon and to the pathologist. In a high grade of adrenal-renal heterotopia the surgeon will find it impossible to effect a separation of the two organs in doing a nephrectomy unless he dissects through renal tissue. He must bear in mind, also, the fact that the condition is often bilateral. If, either by acquired disease or by developmental failure, the remaining heterotopic adrenal is inadequate, death by adrenal insufficiency will ensue. Proper recognition of the gross and microscopic pathology of this condition as met at autopsy will guard the pathologist on the one hand against an erroneous interpretation of it as neoplastic or otherwise and, on the other, will inform him in respect to certain important aspects of the constitutional pathology of the cadaver upon which he is working.

Literature of Adrenal-renal Heterotopia. Rokitsansky,⁸ in 1846, had differentiated acquired inflammatory adhesion between the adrenal and renal capsules from true heterotopia which he characterized as exhibiting a common tunica albuginea investing the two organs. He gave no case report. Since Rokitsansky, most of the important text-books of pathological anatomy have briefly referred to the renal type of adrenal heterotopia.

The first case report in the literature is that of Klebs,³ in 1876, who recorded the occurrence of a thin yellowish layer spread beneath the kidney capsule at the upper end of each kidney. In the usual situations no adrenals were to be found, and microscopical examination showed the thin yellow layer to be made up of cells like those

of adrenal cortex. His patient was a well-developed male, aged twenty years, who died of pneumonia.

A briefly described observation published by Grawitz,² in 1884, came next in chronological order. In a girl, aged two years, adrenals as accessory or supernumerary organs were found at the upper pole of each kidney beneath the kidney capsule. The adrenals themselves were apparently in the normal situation. On the right a portion of the adrenal tissue extended to the depth of 1 cm. in a cleft between two neighboring renal lobules.

In the course of the autopsy of a male, aged sixty-seven years, who died as a result of a cardio-vascular-renal complex, Pilliet,⁶ in 1893, found no trace of the right adrenal in its usual situation. On section of the kidney, however, a yellow plaque was found under the capsule at the upper part of the anterior convexity. Microscopical examination showed this to be adrenal and in some areas there was complete fusion of the two parenchymas. The structure had the appearance of being half of the adrenal only, being made up chiefly of cortical substance, although large bloodvessels, bundles of plain muscle and atrophic groups of medulla cells were found in areas.

In 1895 there were two papers reporting 3 cases of the renal type of adrenal heterotopia. Weinberg¹² recorded an instance in a woman, aged fifty-four years, who died in coma. In attempting to decorticate the kidneys, the renal capsules were found to cover partially a substance identified as adrenal. The right adrenal was united with the kidney for a distance of 3 cm. The left adrenal was united with the left kidney for a distance of 1.5 cm. The remaining portions of the adrenals were free and had the appearance of being enclosed within diverticula of the kidney capsules. Microscopically the adrenals were found to have their own delicate capsules which were lacking completely at certain areas where the parenchyma of the adrenal was in immediate contact with the cortical substance of the kidney. Renal and adrenal tissues were found "côte à côte, parfois se mélangent, mais ne présentent pas d'anastomoses entre eux." No chronic inflammatory changes were found in the kidneys.

In the same year there appeared Ulrich's¹⁰ important paper on misplaced and accessory adrenals in which two examples of adrenal-renal heterotopia were included. The first of these was in a male, aged seventy-two years, alcoholic and demented, who died an asphyxiative death following aspiration. Both adrenals were found spread out in a thin sheet, from 0.5 to 1 mm. in thickness, over the upper poles of their respective kidneys. Upon attempting to remove the kidney capsule, the adrenal was in part removed with it and in part remained adherent to the kidney. No adrenals were to be found in their usual situation. On microscopical examination, a layer of adrenal cortex about 1 mm. thick was found

over the surface of the kidney and separated from it in certain areas only by a connective tissue layer of similar thickness. In some areas the three cortical zones could be recognized, in others only the zona fasciculata. No medullary substance was found. In those areas in which no connective tissue intervened between the two organs, adrenal tissue was found in close association with the urinary tubules.

The second patient of Ulrich's was a male, aged sixty years, diagnosed as a case of psychosis secondary to advanced pulmonary tuberculosis. This the author characterizes as an example of *dystopia partialis glandularum suprarenalium*. The right adrenal consisted of two connected portions, of which the larger was in the form of a flattened mass applied to the anterior aspect of the upper pole of the kidney. The smaller portion was above and apart from the kidney and appeared to be composed chiefly of medulla. Upon stripping off the kidney capsule, the flattened portion of adrenal was found to be left behind, nor was there any loss of substance from the surface of the adrenal from which the kidney capsule came away smoothly. At its inner side the adrenal tissue was found to mingle somewhat with the renal tissue, in such areas no visible connective-tissue capsule intervening. The total thickness of the sheet of adrenal tissue was 1.5 mm. On microscopical examination the zona reticularis was found to be directly upon the surface of the kidney in certain areas and the intimate intermingling of renal and adrenal tissue was fully verified. No medullar tissue was found in this portion of the adrenal. The left adrenal presented in general the same appearances, but was not so intimately united with the kidney.

In 1902 Radasch⁷ reported an interesting case of adrenal heterotopia which probably should be included in our present list. Autopsy verified a clinical diagnosis of gumma of the brain in a male, aged twenty-nine years, who died following a cerebral decompression operation. The kidneys were found to be of normal size. Upon the anterior-superior surface of each kidney a thin yellowish body was found. Each of these covered an irregular area about 3 cm. in diameter and about 1 mm. thick. They were beneath the capsule and in places dipped into the renal cortex. An adrenal of normal size and shape and in the usual location was present on the right side only. Upon the under surface of the liver near the transverse fissure a small, thin, yellowish mass was noticed. It resembled those upon the kidneys and was approximately 1 cm. in diameter and 2 mm. thick. Histological examination of the adrenals in the kidneys showed all three cortical zones with an incomplete capsule between the adrenal tissue and the renal tissue and an intimate mixture of the two parenchymas. Microscopical examination of the mass on the liver showed this also to be adrenal tissue but the relationship was much less intimate, for a thick

layer of loosely arranged connective tissue containing oval masses of adrenal cells separated it from the liver. The reticular zone appeared to be external. The medulla is not mentioned in respect to either situation. Disregarding the hepatic adrenal tissue, which is difficult to interpret from the description, this would appear to be a true instance of bilateral adrenal-renal heterotopia with right unilateral duplication of the adrenal. The presence of additional adrenal tissue on the under surface of the liver serves to connect the cases we are describing with the more common type of aberrant adrenal masses.

Miloslavich⁴ made the most important contribution thus far to the casuistry of adrenal heterotopia in his paper of 1914. In this he added four new examples, reviewed much of the earlier literature and discussed the general significance of developmental disturbances of the adrenal from the standpoint of constitutional pathology. His first patient was a male, aged twenty-three years, who died a respiratory death from bulbar paralysis due to a diffusely infiltrating glioma of medulla, pons and cerebellum, nearly filling the fourth ventricle. There was a marked hyperplasia of all lymphoid tissue and a two-lobed thymus was present. The right adrenal was in the form of a nearly circular disk, measuring 6.5 by 5.5 cm., which was applied to the anterior surface of the upper pole of the kidney. In the central portion this disk was thinned out to such a degree that the adrenal tissue appeared in the form of small isolated islands, while at the circumference of the thinned portion a broad continuous ring of adrenal parenchyma, 0.5 to 1 cm. wide, was present. The left adrenal showed the same changes, but to a somewhat slighter degree. No microscopical description of this case is presented.

His second patient was a male, who died when forty-seven years of age, with a clinical diagnosis of diabetes mellitus and myocardial degeneration. While the thymus was represented by a well-defined fatty mass only and did not appear lymphoid, all other lymphoid structures showed the marked hyperplasia of a status lymphaticus of high degree. The adrenals had the form of nearly circular disks, 5 to 6 cm. in diameter, firmly fixed at the upper pole of each kidney. On removing the kidney capsules the adrenal tissue was left attached to the kidney. On section, the adrenal was found to be very thin, measuring only 1 mm., the lower cortical leaf could scarcely be recognized as such, no limiting layer (capsule) could be found and medullary substance was not recognizable. On microscopical examination the single cortical layer was found to show its three zones well differentiated. In areas it was separated from the kidney parenchyma by a delicate connective-tissue layer which was interrupted entirely for varying distances where the parenchyma of the adrenal came in direct contact with kidney elements. In some sections the adrenal cell

complexes which were mingled with kidney tissue resembled those of the zona glomerularis while others were of the type of the zona fasciculata. The medulla was very sparsely represented by single cells or small groups of cells. The left adrenal showed similar microscopical findings. Rounded and elongated masses of smooth muscle were found in and beneath the kidney capsule, where adrenal and kidney were united, in the zona glomerulosa lying in the kidney and in the central portion of the adrenal.

The third case contributed by Miloslavich was that of a man, aged twenty-six years, with a clinical diagnosis of tuberculous meningitis, found at autopsy to have chronic pulmonary and generalized miliary tuberculosis. There was a persistent hyperplastic thymus, measuring 7 cm. in length and 3 cm. in breadth, and a small thyroid. The left adrenal was broad and thin and united with the upper pole of the kidney. The right kidney was large and presented a double pelvis and double ureters which were united at the level of the brim of the pelvis. The right adrenal was somewhat larger than the left and was attached not only to the upper pole of the kidney but also to the liver. Between the right adrenal and the kidney there was no demarcating connective-tissue layer, while on the left a recognizable separation was present. Between the right adrenal and the liver a slender connective-tissue layer effected a separation. Microscopical examination showed between the right kidney and adrenal a thin connective-tissue layer which became more and more attenuated until it was entirely lacking over extensive areas, permitting the two types of parenchyma to come into immediate contact. Between the left kidney and left adrenal the intervening capsule showed only small defects, and the capsule between the right adrenal and the liver was everywhere continuous. The cortical zones of both adrenals were easily recognizable, but the medullary substance, especially in the right, could not be differentiated with certainty.

The fourth case described by Miloslavich was placed apart from his detailed series, and will be seen to fall into a different category. It should be included here, however, as of importance in establishing one of the varieties of renal-adrenal heterotopia, and should be grouped with the examples from Grawitz and Radasch given above. A woman, aged forty-six years, who died of pulmonary tuberculosis, showed at autopsy a small thyroid, kidneys and adrenals in normal position with the left adrenal closely applied to the kidney and, beneath the capsule of the left kidney, another adrenal measuring 4 by 3 cm. and about 2 mm. thick. There was a plain differentiation of cortex and medulla. No microscopical notes are given. We are not told to what degree the parenchyma of one organ was mingled with that of the other, and no mention of thymus or lymphatic system is made.

More recently (1920) Apert and Vallery-Radot¹ have reported a

typical example of bilateral adrenal-renal heterotopia in a boy, aged six years, who died of tuberculous meningitis. The adrenals were situated anteriorly on the upper poles of the kidneys. Their anterior faces were smooth and they could be distinguished from the kidney substance practically by color alone. Microscopical examination showed a partial admixture of the parenchyma of the two organs and no medullar tissue was found. The thymus was not mentioned.

Literature of Adrenal-hepatic Type. Weiler,¹¹ in 1885, reported the occurrence of the right adrenal upon the convex portion of the surface of the liver, at a distance of but 3 cm. from the fold of the right coronary ligament. From the posterior portion of the main mass a more slender prolongation extended through the capsule and into the substance of the liver to a depth of 5 mm. There was also a close union between the left adrenal and left kidney, the adrenal being situated between the layers of the fibrous capsule of the kidney. The patient was a male, aged twenty-five years, who died of pulmonary tuberculosis.

The case reported by Schmorl,⁹ in 1891, which is considered by Miloslavich as belonging with those in which the entire adrenal is found in or beneath the hepatic capsule, has been misquoted by the latter. It is evident that the masses of adrenal tissue which in this instance were separated from the hepatic parenchyma only by an incomplete septum through which bile ducts could be traced were relatively small accessory adrenals, while the organ proper was found in its usual situation. This case must therefore be excluded.

In 1900, in the course of an autopsy on a female infant, aged one year, Oberndorfer⁵ found the right adrenal adherent in the impressio suprarenalis and apparently separated from the liver by a band of connective tissue about $\frac{1}{3}$ mm. wide. The capsule was thickened. There is no evidence that the parenchyma of one organ was mingled with that of the other. The child exhibited a hypertrophic liver cirrhosis of syphilitic origin. The author, probably rightly, attaches much importance to the chronic inflammatory process in explaining the etiology of the condition. He suggests that there may have been a primary inclusion of the adrenal, with secondary separation of the two organs through connective-tissue proliferation in connection with the cirrhosis; or that through connective-tissue proliferation certain groups of cells may have been snared off and thus come more and more to lie in the accumulating connective tissue between the two organs. He favors the second explanation. In view of the demonstrated inflammatory condition present, this case must be included with reservations, if at all. To the examples appearing in the literature we are able to add cases falling into each of the two main groups—1 to the group of 12 cases of adrenal-renal heterotopia and 3 to the 1 or 2 hitherto

TABULAR SUMMARY OF THE PREVIOUSLY REPORTED CASES OF BOTH TYPES OF ADRENAL HETEROTOPIA WITH ADDITION
OF THE NEW CASES DESCRIBED IN THE PRESENT PAPER.

	Author.	Date.	Heterotopia.	Duplication	Sex.	Age.	Remarks.
1	Klebs	1876	Bilateral adrenal-renal	None	M.	20	Pneumonia.
2	Grawitz	1884	Bilateral adrenal-renal	Bilateral	F.	2	Cause of death not given.
3	Pilliet	1893	Right adrenal-renal	None	M.	67	Cardiovascular renal death.
4	Weinberg	1895	Bilateral adrenal-renal	None	F.	54	Death in coma.
5	Ulrich	1895	Bilateral adrenal-renal	None	M.	72	Alcoholic. Demented. Asphyxiative death.
6	Ulrich	1895	Bilateral adrenal-renal	None	M.	60	Psychosis. Tuberculosis.
7	Radasch	1902	Bilateral adrenal-renal	Right	M.	29	Gumma of brain.
8	Miloslavich	1914	Bilateral adrenal-renal	None	M.	23	Thymico-lymphatic constitution. Glioma of pons.
9	Miloslavich	1914	Bilateral adrenal-renal	None	M.	47	Status thymico-lymphaticus. Diabetes.
10	Miloslavich	1914	Bilateral adrenal-renal	None	M.	26	Status thymico-lymphaticus. Tuberculosis.
11	Miloslavich	1914	Left adrenal-renal	Left	F.	46	Tuberculosis.
12	Apert and Vallery-Radot	1920	Bilateral adrenal-renal	None	M.	6	Tuberculous meningitis.
13	Weller	1924	Bilateral adrenal-renal	None	M.	40	Thymico-lymphatic constitution. Familial diabetes.
1	Weiler	1885	Adrenal-hepatic	None	M.	25	Pulmonary tuberculosis.
2	Weller	1924	Adrenal-hepatic	None	M.	25	Persistent thymus. Endocarditis.
3	Weller	1924	Adrenal-hepatic	None	M.	17	Persistent thymus. Lymphosarcoma.
4	Weller	1924	Adrenal-hepatic	None	M.	61	Persistent thymus. Emphysema.

reported cases of adrenal-hepatic heterotopia (see Table I). For the sake of brevity the protocols of our cases have been abstracted and only the data germane to our present discussion will be quoted. In each instance these will appear in a definite order: Autopsy number; sex; age; clinical diagnosis; habitus of cadaver; gross pathology of brain, thyroid, thymus and lymphadenoid tissues in general, left kidney, left adrenal, right kidney, right adrenal; microscopical pathology of such of these organs as show significant changes; pathological diagnosis.

CASE I.—*Bilateral Adrenal-renal Heterotopia (without Duplication)*. Autopsy No. 1559 (A-62-AB). E. W., male, aged forty years.

CLINICAL DIAGNOSIS. Diabetes mellitus; chronic pancreatitis.

HABITUS.. Cadaver of slender build, exhibiting the asthenic constitution to a marked degree. (The patient comes from a family with an unusual history of severe familial diabetes.)

GROSS PATHOLOGY. *Brain*: no anomalies; no gliosis. *Thyroid*: small. *Thymus*: no thymic parenchyma recognized with the naked eye. *Left kidney*: in normal position and of normal size. *Left adrenal*: spread out in a thin sheet covering the upper pole of the left kidney, particularly anteriorly, and apparently having a common capsule with the kidney. *Right kidney*: normal in size and position. *Right adrenal*: in general, resembles the left and bears a similar relation to the right kidney, but covers a considerably greater portion of the kidney surface, occupying nearly one-half of the anterior aspect as it spreads downward from the upper pole; here, also, a common capsule appears to cover the united organs.

MICROSCOPICAL PATHOLOGY. *Brain*: congestion and edema only; no gliomatous proliferation or sclerosis in areas sectioned. *Thyroid*: marked diminution of colloid; many acini containing no colloid; cells more distinctly low columnar in type than in the normal thyroid, but no parenchymatous hypertrophy of the exophthalmic type; stroma increased, both relatively and absolutely. *Thymus*: abundant remains of thymus; numerous large and calcareous corpuscles of Hassall; atrophic hyperplastic thymus. *Lymph nodes*: marked exhaustion of germ centers. *Adrenals*: sections across the adrenals, including the upper poles of the kidneys, are alike, one description answering for those of both sides. At its upper surface the adrenal has a capsule of its own and at its border it exhibits a rounded edge. At this point it lies separate from the renal capsule for a distance of 2 cm. Leaving the free portion, the renal and adrenal capsules first fuse, then become attenuated, and finally disappear entirely in certain areas. A fused capsule reappears at intervals. Where the capsule is lacking there is an intimate admixture of renal and adrenal parenchymatous tissues, and for part of the distance that half of the adrenal cortex toward the kidney

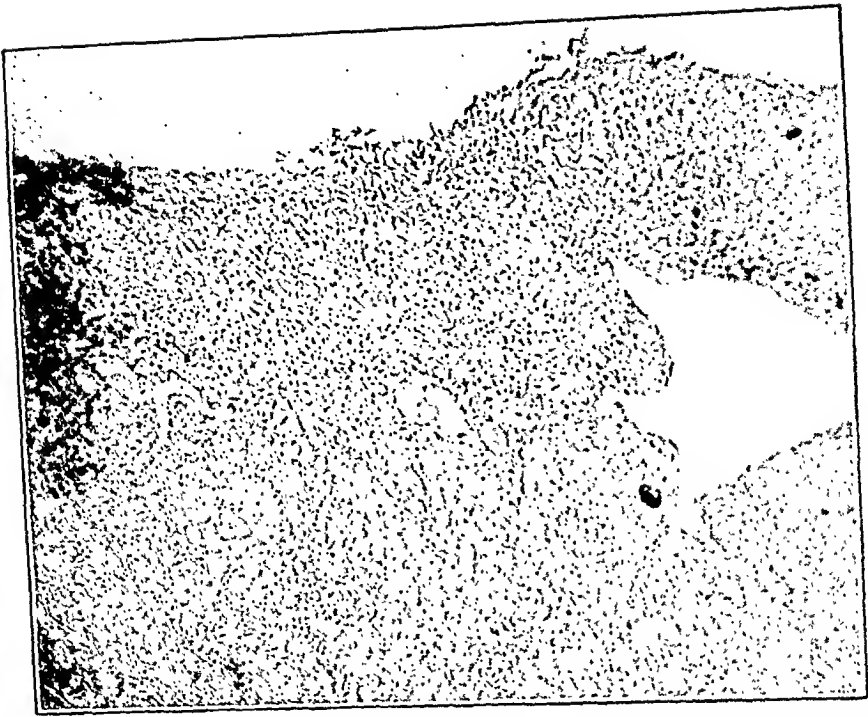


FIG. 1.—Case 1. Adrenal-renal heterotopia. Low-power photomicrograph showing reduction of adrenal to its outer cortical leaf only. This, and an adrenal vein as well, are in intimate contact with the renal parenchyma. (All photomicrographs were made from hemalum and eosin stained sections.)

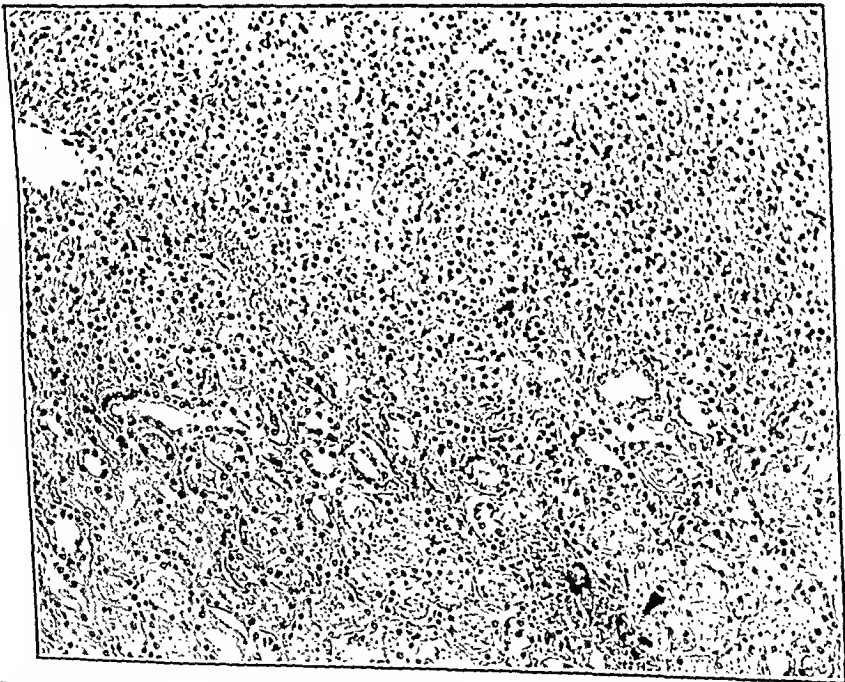


FIG. 2.—Case 1. Adrenal-renal heterotopia. Higher power photomicrograph to show the absence of any connective tissue capsule between the parenchyma of the kidney and that of the adrenal. Renal tubules lie against cords of adrenal cortical cells.

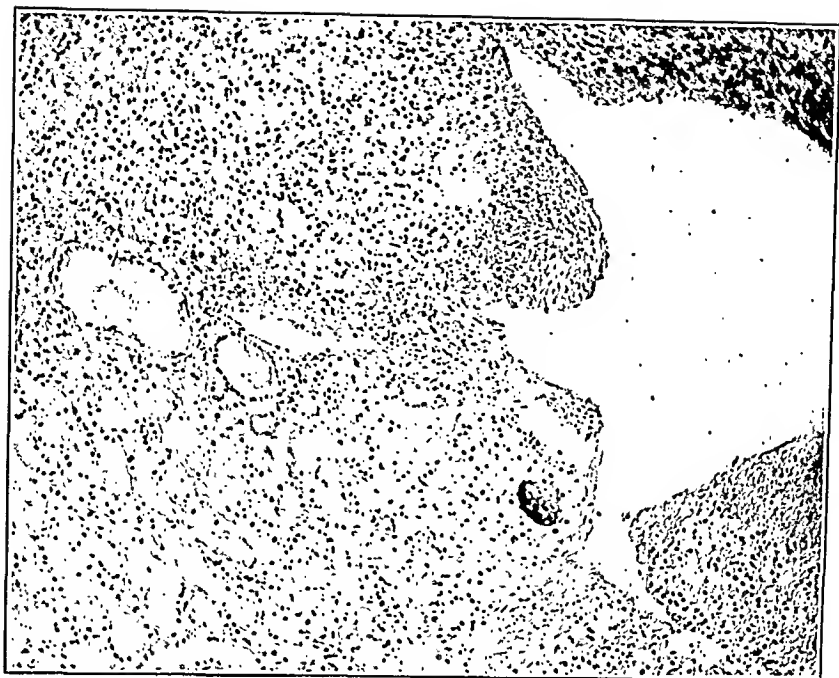


FIG. 3.—Case 1. Adrenal-renal heterotopia. Photomicrograph of an area which shows no limiting membrane between kidney tissue and adrenal. A large adrenal vein is very near the kidney parenchyma indicating the absence of that leaf of the adrenal cortex normally presenting toward the kidney.

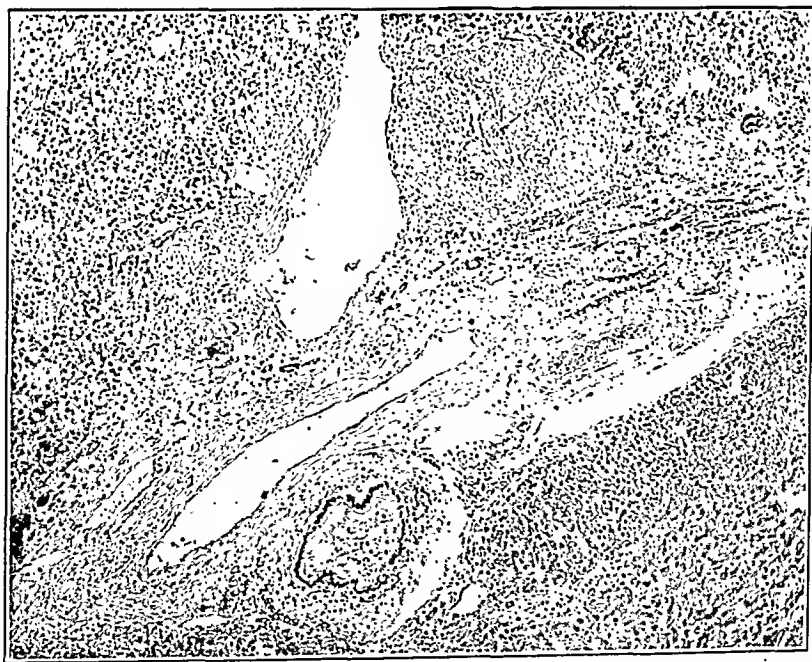


FIG. 4.—Case 2. Adrenal-hepatic heterotopia. Low-power photomicrograph showing adrenal cortex and a large adrenal vein with coarse bundles of involuntary muscle in the upper part of the field. Small bile ducts and a large hepatic trinity are in immediate relationship with the adrenal tissues.

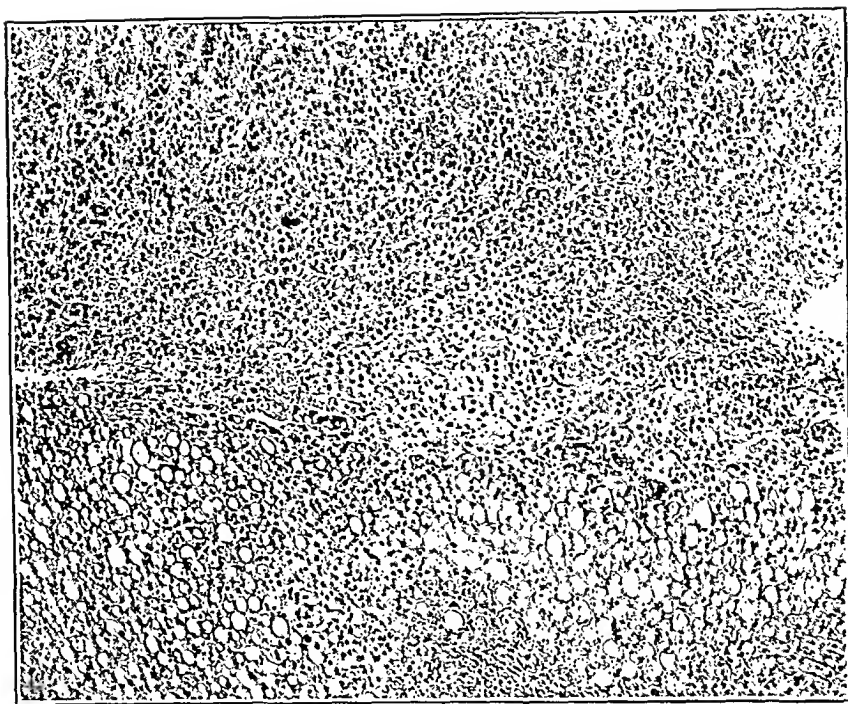


FIG. 5.—Case 3. Adrenal-hepatic heterotopia. Complete absence of any connective-tissue layer between the adrenal and the hepatic parenchyma. The hepatic tissue is sharply differentiated by reason of the fatty change present in it.



FIG. 6.—Case 4. Adrenal-hepatic heterotopia. This case shows a less marked degree of the condition, a few connective-tissue fibrillæ remaining between the two organs. This band appears wider than it should due to traumatic artefact. The proximity of the adrenal vein to liver tissue is proof of the developmental nature of the union between the two tissues.

disappears entirely, bringing the adrenal veins in direct relationship to renal tissue in some areas; while medulla is present in that portion of the adrenal having an independent capsule, through the remainder of the organ medulla is entirely absent; in the areas showing the most intimate admixture the adrenal is therefore represented only by the superficial half of its cortex, that is, the half of the cortex normally farther away from the kidney, and a fibrous capsule which now covers both organs; there is a well-marked lipoidosis of the adrenal cortical cells.

PATHOLOGICAL DIAGNOSIS. Chronic atrophic interstitial pancreatitis (pancreatic insufficiency, diabetes, steatorrhea); marked emaciation; serous atrophy of all adipose tissues; atrophic hyperplastic thymus; heterotopia of both adrenals, with hypoplasia and lipoidosis; pituitary hypoplasia or atrophy, with diminished eosinophile cells; generalized lymphoid exhaustion; hypothyroidism; asthenic constitution; acute staphylococcus serofibrinous pneumonia; multiple pyemic excretory abscesses of right kidney; multiple staphylococcus emboli; severe catarrhal gastro-enteritis; hypertrophy of intestinal musculature; old healed tubular nephritis; early sclerosis of renal arterics; moderate atherosclerosis of aorta; old focal leptomeningitis; atrophy, congestion and acute parenchymatous degeneration of all organs; lymphoid infiltration of periportal tissue; excessive hemolysis in spleen and lymph nodes; eosinophilia of prevertebral lymph nodes; diminished spermatogenesis.

CASE II.—*Adrenal-hepatic Heterotopia (without Duplication).* Autopsy No. 1118 (A-70-Y). L. D., male, aged twenty-six years.

CLINICAL DIAGNOSIS. Vegetative endocarditis (*Streptococcus viridans*) of aortic and mitral valves; aortic and mitral insufficiency; cardiac hypertrophy and dilatation; myocardial degeneration; embolism of spleen; parenchymatous nephritis.

HABITUS. Medium build; intercostal angle much greater than a right angle; type approaches that of the thymico-lymphatic constitution.

GROSS PATHOLOGY. Permission to examine the *brain* and neck organs (*thyroid*) was refused. *Thymus*: no lymphoid tissue recognizable in the thymic fat upon naked-eye examination. *Left kidney*: in normal position; somewhat larger than normal. *Left adrenal*: of normal size and in normal position; moderate lipoidosis of the cortex. *Right kidney*: normal in size and position. *Right adrenal*: upon attempting to remove the right suprarenal it was found to be firmly united to the posterior surface of the right lobe of the liver at the impressio suprarenalis; the usual easy separation between the two organs could not be effected; while the lower pole of the adrenal could be lifted slightly away from the surface of the kidney, the remainder of the gland was firmly fixed, its

capsule apparently uniting with the liver capsule and the greater part of the suprarenal gland substance appearing to be beneath the joint capsule of the two organs.

MICROSCOPIC PATHOLOGY. *Thymus*: persistent; fibroid atrophy but with numerous corpuscles of Hassall; an atrophic hyperplastic thymus. *Lymph nodes*: hyperplastic. *Right adrenal*: throughout the greater part of its length, the adrenal is firmly adherent to the liver, from which it is separated in some areas by a thin connective-tissue band, while in other areas there is no connective tissue intervening between the two organs; small bile ducts occur very constantly within the adrenal parenchyma; through much of the distance the adrenal is represented only by the glomerular, fascicular and reticular zones of its outer one-half; in a few areas only is there any medulla; the zona pigmentosa lies in immediate association with the bile ducts and liver cells of the hepatic parenchyma; along this line a large adrenal vein with its characteristic musculature is in immediate association with a large hepatic vein and bile duct.

PATHOLOGICAL DIAGNOSIS. Chronic aortic thrombo-endocarditis; *Streptococcus viridans* infection; rupture of aortic cusp; mycotic aneurysm in first portion of aortic arch; subacute pericarditis and myocarditis; aortic stenosis and insufficiency; relative mitral insufficiency; cardiac dilatation and hypertrophy; chronic passive congestion of lung with diffuse interstitial pneumonia; multiple infarctions of spleen and kidneys; nutmeg liver; chronic passive congestion of all organs; hydropericardium, hydrothorax, ascites; subacute parenchymatous nephritis with multiple embolic abscesses; serous atrophy of all fat tissues; fatty degeneration of intima of aorta; hepatic heterotopia of right adrenal; aspermatogenesis; melanosis of skin of thorax; secondary anemia; persistent thymus.

CASE III.—Adrenal-hepatic Heterotopia (without Duplication). Autopsy No. 1564 (A-67-AB). E. U., male, aged seventeen years.

CLINICAL DIAGNOSIS. Intestinal obstruction.

HABITUS. Tall slender type; long bones slender and long; intercostal angle much less than a right angle; asthenic constitution.

GROSS PATHOLOGY. Permission to examine the *brain* was refused. *Thyroid*: about normal size; abundant colloid substance; no adenomas. *Thymus*: thymic parenchyma was not recognized as such with the naked eye. *Left kidney*: normal in size and position. *Left adrenal*: normal in size and position. *Right kidney*: normal in size and position. *Right adrenal*: upon attempting to remove the right adrenal it was found to be firmly united to the posterior surface of the right lobe of the liver at the suprarenal impression. The usual easy separation between the two organs could not be effected; only the lower pole of the adrenal could be lifted from the

surface of the liver, a common capsule apparently covering the two organs.

MICROSCOPIC PATHOLOGY. *Thyroid:* excess of colloid substance. *Thymus:* abundant thymic remains with large corpuscles of Hassall; must be considered a hyperplastic thymus. *Right adrenal:* at its free border the right adrenal has a complete but thin capsule of its own, and in this portion medulla is present within characteristic cortical zones; at first becoming a common band of connective tissue between the two organs, this portion of the capsule finally disappears entirely, leaving hepatic and adrenal parenchymas in intimate contact with each other; in this portion no medulla is present—in fact, where the union is most complete the inner half of the cortex, that is, the portion adjacent to the liver normally, has entirely disappeared.

PATHOLOGICAL DIAGNOSIS. Primary intestinal lymphosarcomatosis, involving jejunum in greatest degree, with stenosis and dilatation of portion of jejunum; diffuse peritoneal lymphosarcomatosis; diffuse lymphosarcomatous infiltration of mesentery and retroperitoneal adipose tissues; general marasmus; tiger heart; fatty infiltration of liver; cloudy swelling of kidneys; hepatic heterotopia of right adrenal; hypertrophic thymus; asthenic constitution; colloid goiter; total aspermatogenesis; atrophy, passive congestion and parenchymatous degeneration of all organs.

CASE IV.—Adrenal-hepatic Heterotopia (without Duplication). Autopsy No. 1603 (A-106-AB). P. L., male, aged sixty-one years.

CLINICAL DIAGNOSIS. Pneumonia; empyema; auricular fibrillation; hypertrophy of prostate.

HABITUS. Long slender build; long bones long and slender; thorax long but intercostal angle is slightly greater than a right angle; asthenic constitution.

GROSS PATHOLOGY. *Brain:* negative except for congestion and edema. *Thyroid:* somewhat larger than normal; both colloid and stroma increased; adenomatous areas. *Thymus:* represented by a long strip of fatty tissue only. *Left adrenal:* moderate hypoplasia; increased pigmentation of the zona pigmentosa. *Left kidney:* in normal situation. *Right adrenal:* the right adrenal was found to be firmly united to the under surface of the right lobe of the liver at the impressio suprarenalis and could not be removed apart from the liver; the adrenal capsule appeared to be continuous with that of the liver. *Right kidney:* in normal situation.

MICROSCOPIC PATHOLOGY. *Brain:* edema and postmortem change only. *Thyroid:* colloid goiter; colloid cysts; increase of stroma locally; connective tissue hyaline change and calcification in the stroma. *Thymus:* abundant lymphoid remains of thymus with numerous corpuscles of Hassall; atrophic hyperplastic thymus. *Lymphoid tissues:* no marked hyperplasia. *Left adrenal:* hypoplasia

of both cortex and medulla; medulla substance present in fair amount. *Right adrenal*: a thin connective-tissue capsule common to adrenal and liver is found to intervene between the parenchymatous portions of these two organs; in areas this connective-tissue band becomes reduced to the width of three or four coarse connective-tissue fibers, and into these, cords of liver cells extend; there is no intermingling of the parenchyma of the organs; the branches of the adrenal vein approach this connective-tissue band with no adrenal cortex intervening; in the portion of the adrenal in closest relationship to the liver there is no medulla; as the organ becomes separated from the liver capsule by intervening adipose tissue a hypoplastic medulla appears; the entire organ is hypoplastic.

PATHOLOGICAL DIAGNOSIS. Chronic bilateral empyema, encapsulated on the right side; chronic purulent bronchopneumonia; atelectasis; emphysema; multiple calcified tubercles in lungs and bronchial nodes; aortic atherosclerosis; atrophy, fibrosis and dilatation of heart; coronary sclerosis; chronic purulent prostatitis with fibrosis; chronic hyperplastic cystitis; chronic parenchymatous nephritis with multiple cysts; atrophy and passive congestion of all organs; chronic perisplenitis and perihepatitis; adenomatous colloid goiter; atrophic hyperplastic thymus; adrenal hypoplasia; hepatic heterotopia of right adrenal; dislocation of left shoulder.

Discussion. With our own cases added, we have for analysis 13 cases of adrenal-renal heterotopia and 4 cases of adrenal-hepatic heterotopia, excluding the doubtful case of Oberndorfer. We find at once that the proposed test by which to check the genuineness of this condition, namely, the absence of the adrenal from its usual situation fails us, for in 3 otherwise acceptable cases, those of Grawitz,² Radasch⁷ and the fourth Miloslavich⁴ case, there had been a duplication of the adrenal so that a gland was present in the normal situation. Moreover, these 3 cases complicated by duplication are of three distinct types. The example from Grawitz exhibited a bilateral adrenal-renal heterotopia and a bilateral duplication; that from Radasch, a bilateral heterotopia and a right unilateral duplication; that from Miloslavich, a left unilateral heterotopia and duplication. The other possible combinations will doubtless be discovered and described in course of time.

It is evident, therefore, that while the absence of an adrenal in the normal situation is of value in determining a true heterotopia, the presence of one still leaves open the possibility of heterotopia associated with duplication. In such a case the further test may be applied of requiring the heterotopic adrenal to present the general form and organization of an adrenal. This will exclude the accessory adrenal masses, usually more or less rounded in form, and frequently of small size, which cannot be considered adrenals proper. It is fully appreciated, however, that this distinction is somewhat arbitrary and that there are cases in the

literature occupying a middle ground and indicating that the heterotopic adrenal with complete duplication is but a grosser manifestation of that dissemination which makes it possible to find small accessory adrenals, usually composed of cortex only, in practically every cadaver in which careful search for them is made.

The bilateral adrenal-renal heterotopia is so conspicuous at autopsy and so easily recognized and interpreted that it is clear that the small number (13) of reported examples must be due to the fact that it is a relatively rare condition. It is usually bilateral, this being true of 11 of the 13 cases. It appears to affect males, especially, 10 of the 13 cases having been of that sex. One of the 2 unilateral cases was in a female, as were also 2 of the 3 cases associated with duplication of the adrenal.

Adrenal-hepatic heterotopia, on the other hand, especially in its less complete degrees, might easily be overlooked at autopsy. That we have been able to find but 1 positive case in the literature cannot be interpreted as demonstrating the extreme rarity of this condition. It is more probable that it has been overlooked, or when found, has not been considered of sufficient importance to merit report. That we have found 3 examples of this condition in the last 800 autopsies supports this view. Here, again, the condition seems to be one affecting males particularly, the questionable case of Oberndorfer⁵ being the only one in a female in this group. With the total number so small, however, no firm conclusion on this point can properly be drawn.

Certain anatomical considerations are of interest. The degree of inclusion of the adrenal may vary over the widest limits, from union of the capsules of the two organs to complete inclusion of the parenchyma of the adrenal beneath the capsule of liver or kidney, bringing the parenchymatous structures of the two in immediate relationship, no capsular structure intervening and typical renal tubules or bile ducts, as the case may be, mingling with cords and nests of adrenal cortical cells. When the union is intimate a portion of the adrenal is usually wanting, so that only one leaf of the cortex is commonly found, showing its three layers of which the glomerular zone will be found to be outermost and the reticular zone mingling with the foreign parenchyma with which it is in contact. Medulla is either entirely wanting or is much reduced where the union is close, but the free poles of the same adrenal may show abundant medullar tissue. Large veins with accompanying bundles of involuntary muscle, characteristic of the adrenal, may be found in contact with the foreign parenchyma even when no adrenal medulla cells occur in the same region. In adrenal-hepatic heterotopia liver veins of considerable size may occur in such close proximity to these adrenal veins that it seems probable that some circulatory communication must exist.

It is not within the scope of this paper to discuss the embryology

of adrenal heterotopia. Attention is called, however, to the fact that the union or inclusion must take place early in development, since the partial or complete lack of medulla in many cases indicates that the medulla cells had not migrated into the cortical mass at the time the heterotopia occurred. True adrenal heterotopia in the sense in which the term is here used is a developmental condition. An acquired inflammatory adhesion of the adrenal to either kidney or liver is sometimes noted, and may result in dragging the adrenal somewhat out of its normal position. This probably explains the case of Oberndorfer⁵ which we have accordingly excluded from our list. His patient was suffering from congenital syphilitic hepatitis. Such inflammatory conditions must not be mistaken for the developmental condition.

The most important aspect of adrenal heterotopia is its bearing upon constitutional pathology. Only Miloslavich⁴ has hitherto seen the importance of this side of the question. The earlier writers give us very little information as to bodily habitus, the lymphatic apparatus and the brain, but the cases of Miloslavich and those which we add show how strikingly this condition is linked with the thymico-lymphatic constitution. Every one of our 4 cases had a persistent thymus as did the 3 of Miloslavich in which the thymus is mentioned. This must be interpreted in the light of the same organ interrelationships as the constant finding of a well-marked adrenal hypoplasia, usually affecting the medulla more than the cortex, in all those possessing the thymico-lymphatic constitution. By the same constitutional pathology is to be explained the relatively early deaths of cases of adrenal heterotopia. In our list we find deaths at ages of two, six, seventeen, twenty, twenty-three, twenty-five, twenty-six and twenty-nine. Only 4 of the 17 reached the age of sixty. These individuals have died at an early age because of their pathological constitution which entails increased susceptibility to infection and decreased resistance to extrinsic factors which prove lethal to them but not to the normal individual. When the chief causes of death are investigated we accordingly find a high incidence of infection, especially of tuberculosis, which is mentioned in 5 instances, with 2 cases of pneumonia, including empyema, and 1 of endocarditis. The one case of generalized lymphoblastoma may, from a broad biological point of view, be related to the constitutional pathology, as may also the glioma of the pons and the 2 cases of diabetes as explained below. We are left with but 4 or 5 cases in which the cause of death may not, in the present state of our knowledge, be at least remotely related to the pathological constitution.

From the evidence at hand it appears that the physical habitus of those with adrenal heterotopia is usually of the asthenic type. This in no sense is in contradiction to the evidence of the thymico-lymphatic constitution afforded by the thymus and by the lymph-

adenoid apparatus, for such a bodily habitus is frequently associated with that constitution and by some is included with it.

Miloslavich⁴ was impressed by the fact that when various malformations of the adrenal were studied the developmental interrelationship between brain and adrenal became evident in the large proportion of associated cerebral conditions, particularly brain tumors and brain hypertrophy. Our cases offer no further evidence along this line. That important disturbances of metabolism of endocrinal origin may be associated seems clear. It must be more than a mere coincidence that the list includes 2 cases (Miloslavich, Weller) of fatal diabetes in males aged forty and forty-seven years. Our case came from a family in which other deaths from diabetes in siblings had occurred. This association of bilateral adrenal-renal heterotopia with diabetes should be watched for and made the subject of report. It is possible that a distinct type of diabetes may be present in certain of those in whom adrenal heterotopia is but one indication of a pathological constitution. In our case there were marked changes in the pancreas as well.

The renal type of adrenal heterotopia is of importance to the surgeon, since knowledge of the occurrence of this condition might make it possible for him to spare the adrenal in nephrectomy when otherwise it would be inevitably removed. Notwithstanding the fact that the adrenal is occasionally removed with the kidney in doing a nephrectomy and no ill-effects result, it would seem wise to preserve the heterotopic adrenal for the patient. Such an adrenal is usually, if not always, hypoplastic, particularly in respect to its medulla, and the condition is almost always bilateral. Both adrenals might be necessary to guard against adrenal insufficiency.

The hepatic type of adrenal heterotopia is much less apt to concern the surgeon. The union usually occurs in the impressio suprarenalis and therefore is away from the operative field in gall bladder or duodenal surgery. In view of the wide dissemination of smaller masses of adrenal cortical cells over the liver, and of the case reported by Weiler,¹¹ it is evident that a heterotopic adrenal may be found elsewhere than in the situation mentioned and may be encountered in surgical procedures.

Summary. 1. By heterotopia of the adrenal in liver and kidney is understood the developmental inclusion of the adrenal in or beneath the capsule of one of these organs. Inflammatory adhesions and the lesser aberrant adrenal masses are not included in this definition. Duplication of the adrenal may be present.

2. Of adrenal-renal heterotopia 1 new case is added. This condition occurs chiefly in males and is usually bilateral.

3. Three new cases of adrenal-hepatic heterotopia are added. Although presumably the more common of the two, this has received but little mention in the literature.

4. Adrenal heterotopia is usually associated with a persistent

thymus and other evidences of the thymico-lymphatic constitution, and frequently with the asthenic habitus. It is an evidence of constitutional pathology. Two of the 13 renal cases reported have died of diabetes. In accord with what is known of this constitution, most of the cases of adrenal heterotopia have died at a relatively early age. The incidence of tuberculosis and other infections is high.

5. In adrenal-renal heterotopia the surgeon will inevitably remove the adrenal in doing a nephrectomy unless special precautions are taken. Due to the medullar hypoplasia usually present and the bilateral nature of this condition, it may be especially important that the heterotopic adrenal should not be removed.

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THE PRIMARY MENINGEAL FORM OF SYSTEMIC BLASTOMYCOSIS.

BY C. M. WILHELMJ, M.S., M.D.,

DEPARTMENTS OF BACTERIOLOGY AND PATHOLOGY, ST. LOUIS UNIVERSITY MEDICAL SCHOOL, ST. LOUIS, MO.

SYSTEMIC blastomycosis, the first case of which was reported by Busse and Buschke in 1894, is now recognized as a definite pathological and clinical entity. At the fastigium a typical case is not difficult to recognize, or at least to suspect. The outstanding features are essentially those of pyemia. There is usually an irregular fever accompanied by chills and sweats. The skin and

subcutaneous tissues are often extensively undermined by numerous large abscesses. Involvement of the osseous system is common and frequently widespread. Pulmonary implication is usually an early and characteristic feature, the persistent cough producing large amounts of purulent, often blood-stained, sputum. Pus or sputum mixed with 20 per cent potassium hydroxide will usually reveal the blastomycetes, which appear as yeast-like, double-contoured, budding organisms.

Necropsies have amply demonstrated the systemic nature of the infection, and have also shown that certain organs or systems are more prone to extensive involvement than others. This widespread dissemination is characteristic, and the metastases are now believed to occur principally through the blood stream. In view of these facts it is particularly interesting to note that the brain and meninges, especially the latter, are rarely implicated in the process.

The purpose of the present paper is two-fold: (1) To emphasize the infrequency of meningeal invasion, already commented on by other writers; and (2) to point out a small group of cases, to which the writer will add one of his own, which should be considered *clinically* as the *primary meningeal form of systemic blastomycosis*. In order to substantiate more forcibly the difference between ordinary systemic blastomycosis, with or without meningeal involvement, and the latter type it will be necessary to briefly analyze systemic blastomycosis with particular reference to the onset and the organs involved at autopsy. For this purpose 33 cases of systemic blastomycosis have been selected from the literature, all of which are corroborated by autopsy studies. This small group by no means exhausts the literature on the subject, but is believed to present a fairly accurate, composite picture of the condition.

A. Systemic Blastomycosis.¹⁻²⁴ 1. *Onset or Primary Location.* Stober,²⁵ in a critical study of the condition, states: "It is generally held at the present, from both the clinical and pathological evidence, that the respiratory tract is the atrium of infection in systemic blastomycosis." He also suggests that the cutaneous lesions, which so often initiate the process, are very likely metastases from unrecognized pulmonary foci. He believes that the reversal of this channel of invasion, that is, systemic blastomycosis following the primary cutaneous form, is quite rare, since he finds only 3 cases in which it has been definitely proven.

Among the 33 cases selected for analysis in this paper, 27 (81.8 per cent) began with either pulmonary or cutaneous manifestations (20 pulmonary, 7 cutaneous). In the remaining 6 cases the primary symptoms were not stated in 1; consisted of vague joint symptoms in 3; abdominal pain, vomiting and ascites in 1; a diffuse rapidly spreading infection around a tooth in 1.

2. *Organs Involved at Autopsy.* A statistical study of the organs found involved at autopsy is the most direct route to a reconstruction, *en masse*, of the clinical course of these cases. The results from the 33 cases under discussion are shown in Table I. The importance of skin lesions, from small single pustules to large subcutaneous abscesses, is verified when we see that they were present in 32 out of 33 cases. The 1 case in which skin lesions were absent was atypical in other respects;¹⁶ the antemortem symptoms were principally abdominal, and postmortem examination revealed involvement of the peritoneum but not of the lungs.

TABLE I.—ORGANS INVOLVED AT AUTOPSY IN THIRTY-THREE CASES OF SYSTEMIC BLASTOMYCOSIS.

Organ.	No. of cases.	Per cent.	Organ.	No. of cases.	Per cent.
Skin	32	97	Other bones or joints	17	51
Lungs	30	90.9	Peritoneum	1	3
Kidneys	15	42	Prostate	5	15
Liver	12	36	Testicle	1	3
Myocardium	3	9	Eye	2	6
Endocardium	1	3	Brain	9	27
Pericardium	4	12	Meninges	4	12
Spleen	19	57	Larynx and trachea	3	9
Pleura	7	21	Adrenals	2	6
Lymph glands	11	33	Gastro-intestinal tract	3	9
Pancreas	3	9	Spinal cord	2	6
Vertebra	9	27	Urinary bladder	1	3
Skull bones	7	21			

Next in importance and frequency are the lung lesions, which were present in 30 cases. Granting that the lungs were carefully searched for specific lesions in each instance, we must either assume that the organisms can gain entry through the respiratory tract and be disseminated throughout the body without producing permanent pathological changes in the lungs, or that there are other portals of entry.

Twenty-two cases (66.6 per cent) showed bone lesions involving either the vertebrae, skull or appendicular skeleton. Involvement of the skull bones is of particular interest because of its etiological relationship to meningeal invasion.

Involvement of the abdominal organs is very common and widespread, but actual invasion of the peritoneum, *per se*, is one of the rarest of lesions.

Brain lesions, usually abscesses, were present in 9 cases (27 per cent).

B. Systemic Blastomycosis with Meningeal Involvement. Among the 33 cases of generalized blastomycosis analyzed above, only 4 (12 per cent) were characterized by meningeal invasion.^{26 27 28 29} These cases deserve special mention, and are analyzed separately in order to emphasize the differences between them and the small group in which blastomycotic meningitis occurred without gross

clinical evidence of systemic invasion. The brain and meninges were not examined in all cases of this series, but where clinical evidence of meningitis was not present we are fairly safe in assuming its pathological absence; the figure, however, may be somewhat low on this account.

1. *Onset, or Primary Location.* Two cases began with pulmonary symptoms and proceeded to run the typical course of generalized blastomycosis until the signs of meningitis occurred. One case began with a small pimple near the external canthus of the eye, which finally opened and discharged considerable pus. There was marked edema around the eye and the initial lesion. The fourth case is said to have started around a lower wisdom tooth. A gradual swelling of the whole face occurred, which became so marked that the patient could hardly open his mouth. Some time later the orbit became involved and an enucleation was performed.

2. *Organs Involved at Autopsy.* Table II gives the results of autopsy examination in these 4 cases. The systemic nature of the invasion is confirmed by a study of the organs involved, and only certain features deserve special emphasis. *Every case was characterized by some form of cutaneous lesion. Three cases showed pulmonary lesions and 3 cases had involvement of the skull bones.*

TABLE II.—ORGANS INVOLVED AT AUTOPSY IN FOUR CASES OF SYSTEMIC BLASTOMYCOSIS WITH MENINGEAL INVOLVEMENT.

Organ.	No. of cases.	Per cent.	Organ.	No. of Cases.	Per cent.
Skin	4	100	Brain abscesses . . .	2	50
Skull bones	3	75	Heart (endo-, myo- and pericardium) . . .	1	25
Paranasal sinuses . . .	1	25	Spleen	2	50
Retropharyngeal abscess	1	25	Liver	1	25
Lungs	3	75	Eye	1	25
Vertebra	1	25			
Other bones or joints .	2	50			

In reviewing this brief analysis of systemic blastomycosis, it is apparent that meningeal invasion is not as common as would be expected from the extensive nature of the metastases. Where meningeal invasion has occurred lesions of the skull bones or foci around the head have often facilitated direct invasion by continuity, or short metastases by way of the regional vascular and lymphatic channels.

C. Blastomycotic Meningitis without Clinical Evidence of Systemic Invasion. Six cases are analyzed under this heading—5 found in the literature and 1 case of the writer, not previously reported.

Case Reports. CASE I.³⁰—A woman, aged sixty-three years, who after a period of general feebleness became confused and talkative, was admitted to the Matteawan State Hospital. During two weeks' observation she was in an almost continuous coma-

tose state, with occasional periods of low delirium. At autopsy the brain showed a diffuse pial haziness, more marked over the base than over the cerebrum. The meninges, particularly over the base, showed a remarkable appearance. The organisms were frequently found in large masses or scattered singly, and were more or less mixed with the elements of inflammatory exudate—lymphoid, plasma cells and large numbers of giant cells—which contained the organism. In the lateral ventricles the organism was found with accompanying exudate. Over the base where the reaction was most marked there was no tendency to tubercle formation or caseation. Near the root of the left lung there were numerous cavities filled with a gelatinous mucoid material. This was at first thought to be a colloid carcinoma, but it was later found that the gelatinous masses consisted of the typical large-capsuled budding organisms. *There were no skin lesions. All other organs were negative both grossly and in sections.*

CASE II.³¹—A Chinaman, aged fifty-three years, complained of severe and persistent headache which had been continuous for five weeks. The only other complaint was of failing vision. There was no history of any affection of the skin or of any lung trouble. The pupils were active and equal; the reflexes equal and active; there was no ataxia. The urine was negative. The spinal fluid was turbid and under considerable pressure. *The typical budding organism was found in the spinal fluid.* Shortly before death he became deaf, pupil inequality developed and the patellar reflexes disappeared. The autopsy showed *no skin lesions*. There was a diffuse cerebrospinal meningitis and an acute myelitis of the dorsal part of the cord. *No other organs in the body were found to present any marked abnormality.*

CASE III (Hansemann, quoted by Goto³²).—The man, aged eighteen years, was partially comatose when seen. Examination disclosed a pulse rate of 46, bilateral abducens paralysis, vertical nystagmus, unequal pupils and marked pulmonary tuberculosis. There was vomiting and incontinence of feces and urine. He finally developed delirium and coma, and died in nineteen days. The spinal fluid was at first clear but later became turbid. *The typical organism was found in the spinal fluid, but was at first not recognized as the blastomyces.* The autopsy showed definite and marked pulmonary tuberculosis. The cerebrum and walls of the ventricles were studded with cysts. The same small cysts were found in the meninges. The cysts were small—none larger than a hemp seed. The corpus striatum and part of the optic thalamus were roughened and covered with colloid-like blisters. The pia was infiltrated with lymphocytes and leukocytes. *There were no skin lesions and no other organs were involved.*

CASE IV (Turk, quoted by Goto³²).—A man, aged forty-three years, epileptic since childhood, and operated on for swelling and suppuration of the cervical lymph glands at the age of eleven years, was suddenly seized with severe headache, vomiting and signs of meningitis. There was marked neck rigidity, a positive Kernig sign, but no involvement of the cranial nerves. The spinal fluid was at first only slightly turbid and under moderate pressure; later the turbidity became more marked and the pressure very high. *The organisms were found in the spinal fluid.* Blood and urine cultures were negative. The autopsy showed definite tuberculosis of the lungs and lymph glands. There was a low-grade meningitis which could not be demonstrated as tuberculous, but in which the blastomycetes were found. There was no tubercle formation. A pathological condition of the mouth, pharynx and esophagus was found. In the pharynx the blastomycetes, mixed with fibrinous exudate, were found deep in the musculature. Turk expresses the belief that this pharyngeal focus was primary and that the organisms reached the meninges from here by way of the blood stream. *No lesions of the skin or other organs are mentioned.*

CASE V (Goto³²).—The man, aged sixty-one years, had been feeling somewhat ill and irritable for a short time. He complained of a stubborn coryza which would not yield to treatment. Anosmia and deafness in the right ear were noticed soon afterward. The chief complaint was pain in the right occipital region, which became so severe that it interfered with sleep. Ptosis of the right eyelid and diplopia soon appeared. The headache gradually became worse, and he finally developed nausea, vomiting and dizziness. Urine examination revealed glycosuria. Physical examination disclosed right abducens and right hypoglossal paralysis, with atrophy of the right half of the tongue. The reflexes were equal and active. *The lungs were clinically negative.* The eye-grounds were normal. Spinal fluid was at first clear, but developed a fine flocculent precipitate on standing. It contained no globulin. The spinal fluid later became turbid and under increased pressure. *A culture of the first fluid obtained gave one colony of the double-contoured refractile organism, and simple microscopical examination of subsequent specimens revealed the blastomycetes.* The patient gradually became more somnolent, but the headache was still severe. Both knee jerks and the right ankle reflex finally disappeared. At autopsy the dura was normal. Pia and arachnoid contained numerous small submiliary tubercles. These same small tubercles were found on the choroidal plexus. A complete autopsy was not performed. *No skin lesions are mentioned.*

CASE VI (writer's case).—The man, aged forty-one years, with past history negative, has always been healthy. His habits and living conditions were good.

History of Present Illness. He was first taken sick about two and a half months ago with a "cold in the head;" this was not severe and was unaccompanied by any pulmonary symptoms or cough. During this period he developed earache on the left side which continued until the ear began discharging. After about ten days' treatment the discharge ceased. About this time he began having left-sided headache, most intense over the parieto-temporal area and extending back to the occiput. This headache was very intense, but in spite of it he continued to work for about one month, but was finally forced to give up and go to bed. After resting for about one week he felt better and returned to work. The headache became more intense, and after about two weeks he entered the Deaconess Hospital of East St. Louis, Ill. At the time of entry into the hospital there was no clinical evidence of mastoid involvement. Vertigo did not accompany the headache. Several stereoscopic roentgenograms of the head revealed two constant findings: (1) A diffuse haziness of the left mastoid cells, and (2) a fairly well-defined shadow on the left side, beginning near the mastoid area and extending upward and forward, ending near the sella turcica. Examination of the eye-grounds showed the vessels somewhat engorged but otherwise negative. The left tympanic membrane was somewhat thickened and discolored. On March 17 a mastoidectomy was performed by Dr. W. Boyne. His report states that only a minute amount of pus was found in the antrum, but that the mucosa was thickened and edematous.

The *laboratory findings* were as follows: The Wassermann (blood) was negative in both alcoholic and cholesterinized antigens. Several leukocyte counts averaged about 11,500. Differential count: Neutrophils, 80 per cent; small lymphocytes, 14 per cent; large lymphocytes, 3 per cent; eosinophiles, 2 per cent; basophiles, 0. Before the mastoidectomy the temperature had fluctuated between normal and 100.5° F.

On March 20 the patient was seen in consultation by the writer. Examination showed a well-nourished man, conscious and rational, complaining of severe headache on the left side. *There were no cutaneous lesions.* There was no cough. The pupils were equal; they reacted to light and accommodation, and there was no nystagmus. The tongue protruded in the midline and there were no speech disturbances. There was no neck rigidity. The lungs and heart were clinically negative; the pulse rate was 76. All reflexes of the upper and lower extremities were active and equal. Pathological toe signs were absent; there was no knee or ankle clonus, while Kernig's sign was doubtful. Gross sensory examination was negative. Spinal puncture gave fluid that was water-clear and apparently under normal pressure, with a very faint trace of globulin, and 14 to 18 cells per 1 c.mm. A Wassermann was not done. No organisms were seen.

In view of the history and clinical findings, the most probable explanation was that we were dealing with a brain abscess following otitis media. On March 23 an exploratory craniotomy over the left parietal area was performed by Dr. C. F. Wilhelmj. The brain and meninges appeared normal. Cautious exploratory puncture failed to reveal an abscess cavity. The patient's condition gradually became worse, and death occurred on March 25.

At *autopsy* permission was obtained to examine only the head. The dura was normal, except for congestion and edema around the operative site. Pia and arachnoid over the vertex were congested and edematous, especially on the left side (site of operation). On the base, especially around the optic chiasm, anterior perforated

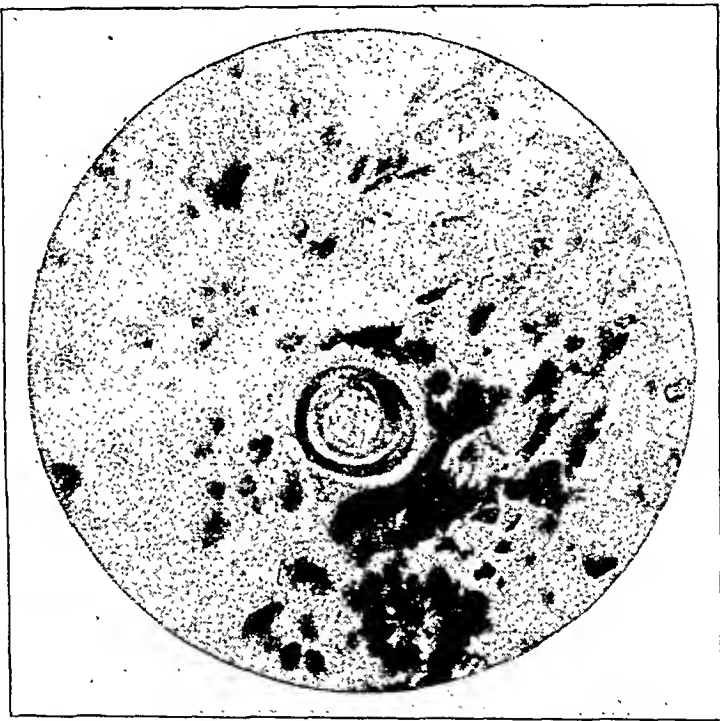


FIG. 1.—A single organism as seen under high magnification.

space, and over the pons, the pia and arachnoid were studded with numerous very minute tubercles of a grayish-yellow color. There was no exudate. Sections through the brain failed to reveal any abscess formation. From these findings a macroscopical diagnosis of tuberculous meningitis was made.

Microscopical examination of the pia and arachnoid from the base of the brain showed round-cell infiltration, collections of giant cells and numerous double-contoured budding yeast-like organisms, which showed no evidence of endosporulation (Figs. 1 and 2).

The portal of entry of the infection in this case is uncertain; most likely it occurred through the upper respiratory tract during

the initial period of eoryza, but the possibility of a blastomyeotic infection of the middle ear cannot be definitely exeluded, since no cultures or microscopical examinations were made from the discharge.

An analysis of these 6 cases yields the following interesting and important data which differentiate them clinically from the usual ease of systemic blastomycosis, with or without meningeal implication: (1) *Skin lesions were absent in all cases*; (2) bone or joint involvement, so common in ordinary generalized blastomycosis, was not present in a single case; (3) necrosis and destruction of the skull bones, apparently an important etiological channel for meningeal infection in systemic blastomycosis, was not a factor in these

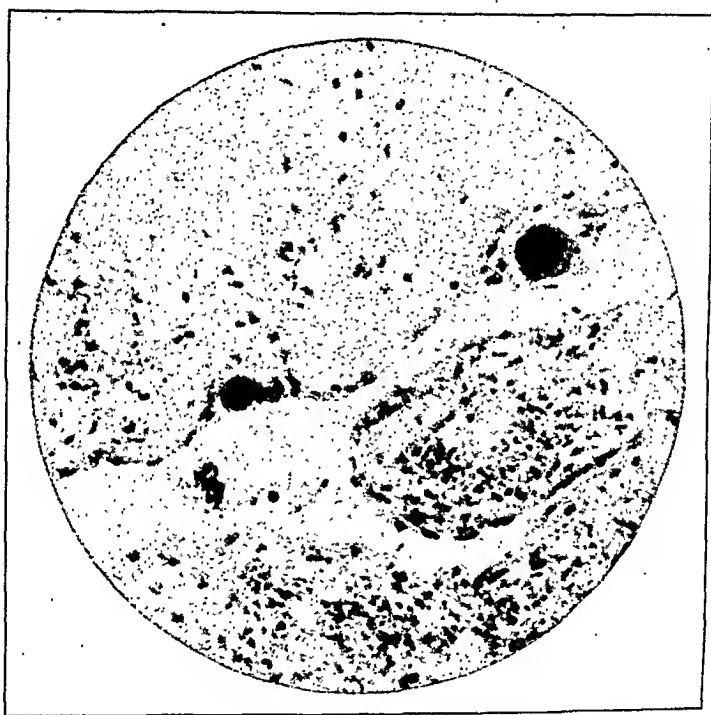


FIG. 2.—Low magnification, showing two organisms.

eases; (4) the organism was found in the spinal fluid of 4 cases; (5) complete autopsies were performed in 4 cases (in 2 of these no mention is made of blastomyeotic lesions in any other organs, the lungs were involved in 1 and the mouth, pharynx and esophagus in the fourth); (6) the 2 incompletely autopsied cases gave no clinical evidence of pulmonary or other organic invasion.

Conclusions. While the 6 cases of blastomyeotic meningitis analyzed in this paper are in many respects very different from the usual ease of systemic blastomycosis, it is doubtful whether or not these differences are of a fundamental nature. There is no substantial evidence to show that the portal of entry, the causative

organism, or other etiological factors, belong to a separate category. The divergence of the clinical course and pathology is no doubt due to the fact that when the meninges are infected during the initial period of invasion, death usually occurs before the typical, extensive, metastatic foci become established. In an etiological sense, therefore, this group probably does not deserve separate classification. Practical clinical classifications, however, should be devised with a view toward their utility in diagnosis, their scientific accuracy being superseded only by this aim. From this viewpoint we are fully justified in recognizing a *primary meningeal form* of systemic blastomycosis which may occur without gross clinical evidence of systemic invasion.

In conclusion, I wish to thank Dr. C. F. Wilhelmj and Dr. W. Boyne for their kind permission to publish the above case of blastomycotic meningitis, and Dr. D. H. Dolley, Professor of Pathology, St. Louis University Medical School, to whom I am indebted for the microscopical diagnosis.

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PRIMARY INOCULATION TUBERCULOSIS OF THE SKIN WITH METASTASIS TO REGIONAL LYMPH NODES.*

By JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

DURING the last eight years, 10 cases of undoubted, and 2 of probable, inoculation tuberculosis of the skin were observed in the Section on Dermatology and Syphilology of the Mayo Clinic. This group constitutes a definite but unfamiliar type of the disease. A better acquaintance with the clinical characteristics of this lesion would result in the identification of more cases, especially by those who, as surgeons, internists, pediatricians, and roentgenologists, are required to deal with superficial tuberculous adenopathies. The demonstration of illustrative cases from this series before the staff of the Mayo Clinic has resulted in the identification of new cases, several of them among physicians and veterinarians.

Inoculation tuberculosis of the skin is known to most physicians as the so-called postmortem wart or verruca necrogenica, a local lesion in the skin usually interpreted as the reaction of a resistant person to inoculation with the bacillus of tuberculosis; in other words, a superinfection. The animal homologue, in which the infected guinea-pig becomes immune to glandular metastatic tuberculosis following inoculation with the bacillus of tuberculosis, even though a local lesion develops, on reinoculation is familiar to experimental workers with this disease. Tuberculosis verrucosa cutis should then, theoretically at least, be the typical reaction of the previously-infected adult to a cutaneous inoculation; and involvement of adjacent lymphatic structures, or systemic infection, should be and is, rare from this type of lesion. Inoculation tuberculosis of the skin, with extension to lymph nodes, and systemic infection should, in theory, be possible only in infancy or early childhood, before systemic infection has developed resistance.

That this immunological rule cannot be applied too strictly to the human problem of inoculation tuberculosis, has been evidenced by the gradual accumulation in the literature of a group of reports describing primary tuberculous inoculation and lymphatic metastasis, in some cases with generalization of the infection, in adults who could scarcely have escaped previous tuberculous infection. Naturally enough, most of the reported cases of this type of tuberculosis are in infants and children. But the demonstration of a group of cases in supposedly resistant adults indicates that the problem of immunity to tuberculosis is, like that of resistance to

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syphilis, not to be summed up by presupposing a resistant or susceptible host and a standard organism, but involves, as Jadassohn¹⁵ well expressed it, the consideration of an almost infinite range of interplay between the susceptibilities of the host and the virulence or avirulence of strains of infecting bacilli of tuberculosis. The complexity of the problem is exemplified by the variety in the results of subcutaneous inoculation, in that in one case it may result in an indolent inflammatory lesion like the verruca necrogenica, in another in the formation of a few tubercles in the fat at the inoculation site and a rapidly developing tuberculous adenopathy, while in a third, there may be a violent inflammatory reaction at the point of entry, which destroys all traces of the organisms but does not occur in time to prevent lymphangitis and adenitis beyond the lesion.

Clinically, tuberculosis verrucosa cutis and primary inoculation tuberculosis of the type described can be quite sharply differentiated. The verrucous form consists of a warty, horny inflammatory papule with villi studding the surface. On pressure small amounts of pus can sometimes be made to exude between the villi. There is little deep infiltration, most of the activity being confined to the upper corium in association with the verrucous changes in the epidermis. In the primary inoculation tuberculosis discussed here, there is no verrucous hypertrophy. The essential lesion is a tubercle rather deeper than that in the verrucous form, better defined and less involved in general tissue reaction. The lesion, clinically, is usually flat, and consists of a group of miliary nodules around a central slightly depressed scar or superficial ulcer. In a few cases there may be deep induration and slight swelling, but as a rule even these are absent. It is the inconspicuousness of the primary inoculation that so often permits it to escape attention in the more active consideration of its consequence.

The Literature. The report by Tscherning²⁴ before the first session of the Congress for the study of tuberculosis at Paris in 1888 furnishes one of the early examples of this type of tuberculous infection. A servant, attending a tuberculous master, wounded a finger with a fragment of sputum cup. Lymphatic involvement followed and it was necessary to amputate the finger and remove the affected glands before recovery ensued. Bacilli of tuberculosis were demonstrated in the tendon sheath. Lennander,¹⁷ in 1889, reported on a tuberculous inoculation apparently following small-pox vaccination in early childhood. Hartzell¹² in 1898, reported 3 unusual examples of inoculation tuberculosis of the hand and fingers, but the lesions were apparently of the verrucous type. Jadassohn,¹⁵ in his authoritative and complete review of tuberculosis of the skin in the *Mracek Handbuch* (1907), mentioned in brief descriptive terms the types of inoculation tuberculosis of the skin designated as tuberculous chancre and epithelioma-like tuberculous indurated ulcers; but the picture of primary inoculation as

here described was evidently not then clear-cut even to an author of such large experience. In 1909 Escherich⁹ reported an inoculation tuberculosis of the cheek in a child, as part of his consideration of inoculation portals for the disease in nurslings. Epstein⁸ (1912) described 2 cases of inoculation tuberculosis of the ear in children following puncture for ear-rings. These 2 were characterized by fulminating local reaction and the destruction of the lobule of the ear, but no generalization of the process. In 1913, Holt¹⁴ reported a case of tuberculosis of the foreskin and penis, with fatal outcome from tuberculous meningitis, following ritual circumcision. His summary of the earlier literature of this form of inoculation tuberculosis, included an instance in which one person had been responsible for the infection of 10 children. Of the 41 patients considered, 16 had died and 13 recovered, the remainder having been lost sight of. The local tuberculous reaction appeared within a week, lymphatic involvement within two or three weeks, and systemic generalized infection, if it occurred, about the third or fourth month. The best results followed the removal of affected lymph nodes. Most of the cases were regarded as syphilitic infections at the outset.

A wave of reports and references to the literature appeared between 1910 and 1914. Brault,³ Curschmann,⁵ Hamburger,¹¹ and Boeck² cited cases of vulvar tuberculosis in children, with inguinal adenitis, resulting from playing on infected floors; Baumel¹ reported cases of tuberculosis inoculated on eczematous lesions. An inoculation on the forehead of an eight-weeks' old child was reported by Scheltema,²³ and the case of a child of fifteen months who developed primary tuberculosis on the thumb, with a large axillary bubo, was reported by Boeck. Chancellor⁴ described 2 excellent cases of primary inoculation tuberculosis, 1 of them from the practice of the late John B. Murphy. In 1 case the primary lesion on the cheek which was followed by lymphatic metastasis, was directly traced to the playful bite of a nurse. On examination her sputum was found to teem with bacilli of tuberculosis. In the other instance, a child's cheek was infected by a scratch from a pin which had been carried between the lips of a tuberculous uncle who often fondled and kissed the child. Lipschütz,¹⁸ in 1914, discussed the possibility that local tuberculous inoculation of the skin might be traced not infrequently to avian bacilli, and emphasized the large number of organisms to be found in such lesions. In 1914 Romer²² stated that the study of the question of tuberculous infection through the skin was still in its beginning and that its frequency could not, therefore, be estimated.

In 1921, following the hiatus of the war, Ravenel²¹ described 3 examples of inoculation tuberculosis, in 1 of which the accidental incision, after being cleansed with mercury bichlorid, healed and did not break down for three weeks. None of these cases, however, seems to have been accompanied by lymphatic metas-

tasis. In the same year Davis⁶ reported a case of inoculation tuberculosis following cat-bite. Dietl⁷ described an excellent case, in which a sixteen-months' old child, whose mother had tuberculosis, was brought to the hospital for examination as a precautionary measure. The child was normal and the von Pirquet and three subcutaneous tests were all negative. Two months later the child was again brought to the hospital with impetigo of the feet and an ulcer 1.5 by 2 cm. on the back. A mass of enlarged lymph nodes had appeared in the left axilla following the development of the ulcer. On excision the lesion was found to be tuberculous. The von Pirquet test was now positive, but there was no other evidence of systemic tuberculosis. In 1922, Lutz¹⁹ presented an excellent summary of tuberculosis of the skin, with a degree of attention to primary cutaneous inoculation that indicates the growing appreciation of the interest and importance of this variety. Hochstetter,¹³ in 1923, reported an example of verrucous tuberculosis on the wrist with what he believed might have been evidence of generalization in the form of tuberculous epididymitis. Joyce,¹⁶ in 1923, described 2 clear-cut cases, of a mother inoculated on the chin and her child on the cheek, presumably by the tuberculous father. The most recent report is that of Nixon and Short²⁰ (1923) in which 4 cases of so-called tuberculous chancre were described. The first was that of a mother who sustained inoculation on the chin with formation of a papule and development of a submental adenopathy, apparently from the kiss of her tuberculous son. The second was a child aged six years who, following a cut over the patella which did not heal for six months, developed an enlarged lymph node in the groin. Tuberculosis was demonstrated in both lesions and uneventful healing followed excision of ulcer and node. The third patient, a child of thirteen years, developed an inflammatory reaction of the eye and a hard nodule at the outer canthus following a blow on the cheek. What seemed to be miliary tubercles appeared along the palpebral conjunctiva, and the nodule broke down. On excision it was found to be tuberculous, and recovery followed. The fourth case is of especial interest because the nodule on the upper lip, which followed a bruise on a small vesicle at that point, after rapidly enlarging, responded promptly to neoarsphenamin administered on the supposition that the lesion was a syphilitic chancre. On excision it was found to be tuberculous.

Efforts to ascertain the frequency of primary inoculation tuberculosis of the skin have resulted only in the finding of a quotation by Epstein from a report by Ghon,¹⁰ of 2 cases of caseous tuberculosis of the preauricular nodes in 184 necropsies on children. In these cases there seem to have been signs suggestive of a cutaneous portal of inoculation.

It will be apparent from even this partial review of the literature that the picture of primary inoculation tuberculosis of the skin

(excluding tuberculosis verrucosa cutis) has been gradually taking form over a period of years, and that a type with varying, and sometimes slight, degrees of local reaction but important extension to adjacent lymph nodes, is assuming distinct definition. In order the more clearly to delineate the type and to illustrate some of the diagnostic problems involved, condensed reports of 10 cases are presented.

Reports of Cases. Three types were recognized: Inoculation on the face, illustrated by 5 cases; inoculation on the forearm or hand, illustrated by 3 cases; and inoculation on the foot, illustrated by 2 cases. Two patients had what seemed to be tuberculous lesions of the umbilicus, whose right to be called an inoculation focus is as yet undetermined. In contrast to the tenor of the literature, only 3 of the patients were young children, two, four and five years of age. Three were adolescents, thirteen, sixteen and seventeen years. Four were adults, all of them over thirty, and 2 nearly or over forty years. There were 5 males and 5 females. Most of the patients were in the best of health at the time of infection, to all outward appearances, only 1 child being sickly following measles. The relatively benign character of the infection was apparent from the continued good health of the patients, the absence of signs of generalization of the infection, and the good response of the majority once a technic of treatment had been developed. Complete studies were not made on the earliest case, because it was not promptly diagnosed. But taking the group as a whole, the tuberculous nature of the condition was carefully checked by clinical and laboratory tests, including animal inoculations, and exclusion of syphilis. Sporotrichosis and actinomyces were later excluded by cultural and microscopical methods, respectively.

CASE I.—A boy, aged two years, seen in 1917, presented a massive swelling with a number of discharging sinuses over the right preauricular and cervical regions (Fig. 1) and temperature of 101.4° F. The first involvement had appeared above the parotid gland five months previously, and had progressed downward, with successive incisions for drainage. Above the right malar prominence was a small depressed scar-like lesion, about 1 cm. in diameter, around which a few apple-jelly nodules could be demonstrated by diaseopic pressure. No information as to the origin or course of this lesion was obtainable. Bacilli of tuberculosis were present in the caseous material and discharge from the lymph nodes. Tonsils and adenoids were enlarged, but except for slight bronchial thickening, the lungs were clear. The child's general health had remained good. The examination of the mother was incomplete, but it was noted that roentgen-ray examination of her chest showed tuberculosis of both apices. Following tonsillectomy, adenoidectomy, and

partial excision of the cervical nodes, with coincident administration of six intravenous injections of neoarsphenamin for its non-specific effect, rapid improvement followed. Ten months later the child was gaining steadily, and roentgen-ray treatment of the nodes was advised.

Although the cart was placed before the horse in the diagnosis of this case, the lesion on the temple being regarded as auto-inoculative or metastatic, and the correction only made in retrospect, all the essentials for a presumptive diagnosis of primary inoculation tuberculosis, except the time sequence, were present. Attention should be particularly drawn to the primary lesion, a small scar-like depression with the so-called apple-jelly nodules in the faintly pink areola of slightly-inflamed tissue around the scar. A few such nodules persisted in the scar itself.

The apple-jelly nodule, on whose identification at the site of inoculation the clinical diagnosis will often depend, is a tubercle in the deeper layers of the corium or in the fat, which though ordinarily invisible in the pink or red of the inflammatory base, can be detected by expressing the blood from the tissue with a glass spatula, the lip of a tumbler, or even a microscopical slide. When viewed thus, the brownish translucent miliary tubercule, 1 or 2 mm. in diameter, stands out clearly against the pale background. Apple-jelly nodules, so-called on account of their color, are not absolutely characteristic of cutaneous tuberculosis, for coarse ones may be found in certain tuberous and nodose hypertrophic syphilids. In general, however, they are a helpful guide to diagnosis, and often the first feature to arouse suspicion at a site of traumatic inoculation. In Case I, the successive involvement of parotid, cervical and submental glands suggests the usual course of lymphatic metastasis from a cutaneous lesion.

CASE II.—A girl, aged seventeen years, seen in 1917, complained of an ulcer on the left cheek of six-months' duration (Fig. 2). On examination it was found to be partially healed, forming a plaque over the left zygoma whose center was covered with epithelium and whose periphery was marked by scattered apple-jelly tubercles. Just anterior to the left ear was a subcutaneous bluish infiltration, and just below this the anterior auricular lymph node had broken down. The node had been drained, but no stain had been made for bacilli of tuberculosis. Although the patient was pale and the right apex showed slightly increased fremitus, the general examination gave no evidence of systemic infection. Three hundred milligram-hours of radium and a curettage of the lymph node failed to afford relief. The primary lesion was excised as epithelioma, after her departure, according to a letter received.

The study of this case must be regarded as incomplete, but its clinical details accord with subsequent observations of other cases.

CASE III.—This was the first example of inoculation on the foot in the series and although primary lesion and metastasis were far apart and not visibly connected, it was possible satisfactorily to relate the two by clinical and laboratory evidence. A boy, aged five years, seen in 1919, had developed a mass in Scarpa's triangle, following a fall. In order to indicate how completely the history of a case may mislead an examiner, the following literal transcript is made: "This child has always been strong and robust. Two months ago he was supposed to have injured the inner side of the thigh riding a tricycle. After a few weeks a lump appeared at the point of injury, tender but not inflamed. It gradually enlarged. After a poultice had been applied for some time the lump softened and opened up with slight discharge. The child was now operated on, a growth the size of a hen's egg being removed, and reported to be a lymphosarcoma. It has always been noted that scratches and abrasions heal slowly." No note was made of any other injury than the fall. The operative wound failed to heal and a chronic ulcer formed. A search for a primary lesion, following a report of inflammatory tissue in a section from the ulcer, revealed the inoculation focus on the great toe. Thereupon, further questioning of the mother recalled the fact that the boy had had a small infected lesion at this site which was opened and drained two or three weeks before the trouble in the groin, and subsequent to the fall from the tricycle. The primary tuberculous lesion thus identified consisted of a group of apple-jelly nodules, with only the slightest surrounding inflammatory reaction, around a healed cut on the inner side of the left great toe. A section including several apple-jelly nodules was then taken from the inoculation site and typical tubercles demonstrated histologically. Radium to the toe and the lymph nodes resulted in rapid healing and the boy was reported in good health six months later. The von Pirquet test was strongly positive at the time the diagnosis was made, but no other evidence of systemic tuberculosis was found.

CASE IV.—This was the third instance of inoculation on the face, and presented several puzzling features. A boy, aged four years had run a stick into his left tonsil ten months before examination (1920). Two or three days later the mother noticed a small lump under the skin of the sternocleidomastoid region. Coincidentally a small pustule on the left cheek about 5 cm. above the angle of the mouth was noticed. The lump on the neck increased in size, softened was opened, healed and broke down again three weeks after an attack of measles. Since the measles the child had been sickly, with occasional fever and vomiting, and had suffered what was regarded as an attack of unilateral "mumps." This apparently consisted of a marked rapid enlargement of the lymph nodes on the left side of the neck with profuse discharge from a sinus. There was no



FIG. 1

FIG. 1.—Probable primary inoculation site on right temple (Case I) with metastatic tuberculous lymph nodes.



FIG. 2

FIG. 2.—Primary inoculation tuberculosis (upper lesion) with typical broken down metastatic lymph nodes. Note the miliary tubercles in the margin of the tuberculous lesion, and the depressed scar-like center.

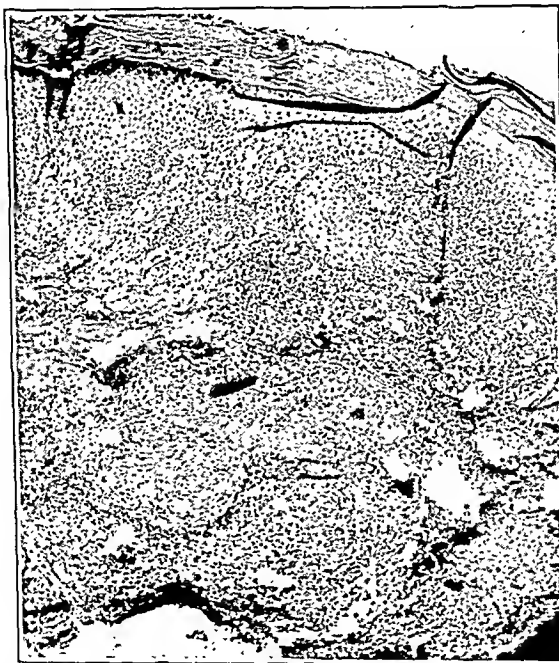


FIG. 3.—Tissue from the primary inoculation site on the great toe (Case III). Note the typical tubercles deep in the cutis, which could be seen as apple-jelly nodules under glass pressure.



FIG. 4



FIG. 5

FIG. 4.—Tuberculous lymphangitis of the upper brachial lymph channels leading to a softened axillary lymph node. The primary lesion is shown in Fig. 5. The lymphangitis could be recognized only on raising the arm, and was indolent and non-inflammatory (Case V). The same condition developed in Case IX.

FIG. 5.—Primary focus on the forearm, of one year's duration (Case V).

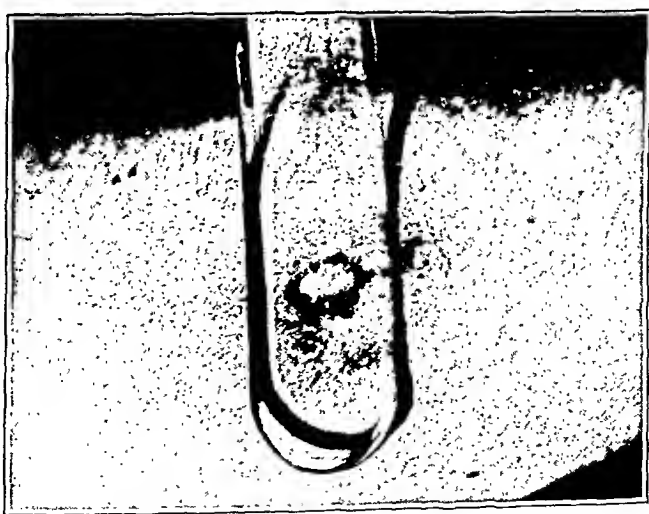


FIG. 6.—Effect of glass pressure in bringing out the barely visible ring of tubercles (apple-jelly nodules) in the scar.



FIG. 7.—Note the scar at the site of the tuberculous glands in the left Scarpa's triangle, removed at operation (Case VI). Four months later, after a recurrence, the primary focus was discovered on the left great toe, as indicated by the pointer.

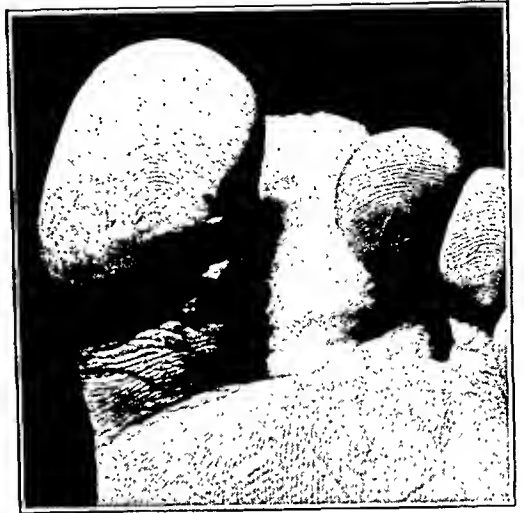


FIG. 8.—Tubercles in the border of the healed scar of a cut on the ball of the toe (Case VI). Metastasis occurred to the lymph nodes in Scarpa's triangle.



FIG. 9.—Primary inoculation tuberculosis on the cheek of a young girl (Case X). There was a nodule over the ramus of the jaw, and a slightly enlarged node just below the ramus.



FIG. 10.—Effect of four months' treatment of the lesion shown in Fig. 9, using the Kromayer lamp with pressure, general ultraviolet irradiation, and neoarsphenamin intravenously. Diagnosis confirmed histologically, syphilis and sporotrichosis excluded.



FIG. 11.—Sporotrichotic primary inoculation of the upper lip, confirmed culturally and disappearing under iodid. Note the chain of metastasis.

familial or contact history of tuberculosis. The focus on the left cheek consisted of a small dry crateriform scar-like depression midway between the zygoma and the left labial commissure, with typical apple-jelly nodules scattered about the immediate periphery of the lesion. Below the ramus of the left jaw was a sinus leading to an enlarged lymph node. There was little or no discharge, and through oversight neither cultures nor stained smears were made. The von Pirquet test was negative, and the chest, which at first showed some hilus infiltration, was reported normal three months later. No sulphur bodies could be found. The diagnosis of primary inoculation tuberculosis remained clinical therefore, and the patient was treated with radium. Complete healing and no recurrence was reported a year later after the application of 1040 milligram-hours of radium to the neck, and 575 milligram-hours to the primary lesion.

In view of the negative von Pirquet test, which, however, was not repeated, and the incomplete laboratory study, this case may remain *sub judice*, although the morphological appearance of the cutaneous lesion was typical of the series. The tonsillar injury gave the impression of coincidence rather than cause.

CASE V.—This case, seen in 1921, was the first of the series showing infection on the arm, and occurred in a veterinary surgeon, aged thirty-nine years, who sought relief from a draining sinus in a softened node in the right axilla. His discomfort was due as much to the sense of tenseness and difficulty in extending the arm, as to the discharge itself. There was no familial history of tuberculosis or of contacts with human tuberculosis, but the patient was constantly exposed to bovine and avian infection in the course of his operative and postmortem work. The dermatological consultation had been called to consider the advisability of using arsphenamin in preference to surgical excision of the node. On further examination, a pipe-stem indolent lymphangitis was found to explain the discomfort on movement of the arm. The cause of the difficulty did not become visible until the arm was fully extended above the head (Fig. 4). On search for a primary focus a small discolored scar-like patch was found on the extensor surface of the forearm, the remains of a nodule that on its appearance a year before, had been cauterized with phenol and iodine and subsequently disappeared (Fig. 5). In the center of this scar, under glass pressure (Fig. 6), a ring of about a dozen small apple-jelly tubercles, acting as the feeder focus for the lymphangitis and adenitis, was identified. The epitrochlear lymph node was only slightly enlarged. The excised axillary node showed typical tuberculosis with caseation, and the widely excised primary focus on the forearm also showed typical tubercles. A few acid-fast organisms were found in the skin sections. Inoculation of guinea pigs was not successful, the animals

dying from secondary infection. Inoculation of hens and roosters was negative.

The treatment in this case consisted of excision of lymph node and primary lesion, the latter being removed down to the fascia; one course of 5 injections of neoarsphenamin, and 33,356 milligram-hours of radium to the axilla and along the course of the involved lymphatics and the excision scar. Slight edema of the hand developed and disappeared uneventfully. A year after diagnosis the patient developed an ischiorectal abscess which did not appear to be tuberculous and which healed promptly after simple drainage. At no time either on first examination or subsequently, during a three-year period of observation has there been any sign of systemic infection.

CASE VI.—A boy, aged thirteen years, seen in 1921, was the clinical twin of Case III, seen in 1919. This previously healthy youth had developed a mass in the inguinal region which broke down and discharged three weeks after the healing of a cut on the outer aspect of the left great toe. The connection with the injury was more easily traced than in Case III. The toe had been cut by a piece of tin and had healed without complications, but a mass about 5 cm. in diameter had appeared in the groin just three weeks later. This had subsided of itself but had lately recurred. The scar on the toe had likewise shown signs of renewed activity, having opened and drained one month before the patient came to the clinic. A surgical diagnosis of tuberculous adenitis, confirmed by pathological examination and positive guinea-pig inoculation from the excised lymph nodes in Searpa's triangle, was made, but the primary lesion on the toe was overlooked. There was a recurrence of the adenitis four months later, this time in the inguinal region, and dermatological consultation was then called to consider arsphenamin as adjunct treatment. The primary focus on the great toe (Figs. 7 and 8) was then found and the presence of apple-jelly tubercles demonstrated in the healed scar by glass pressure and in the excised tissue following biopsy. Guinea-pig, rabbit and chicken inoculations from the toe were negative. Microscopical examination of the skin from the focus showed the tubercles to extend much more deeply into the fat than the biopsy excision, so that an almost complete dissection of the soft tissues of the ball of the toe was then necessary, though it delayed healing somewhat. Large doses of radium, two roentgen-ray exposures, and a course of 8 injections of arsphenamin were employed, with apparently complete recovery during a two-year period of observation. The only ascertainable connection with a source of tuberculous infection was a sister who had had Pott's disease, but who had been away from home for some time.

This case, like others later, furnishes an excellent example of the continued vicious activity of the "feeder focus" and of the benefit

derived from its removal with the recognition of the lymphatic metastasis.

CASE VII.—This case was diagnosed by the Medical Division of the Clinic following the demonstration of Cases V and VI before the staff. A woman, aged thirty-four years, who had a carcinoma of the cervix diagnosed and operated on in 1920, returned in 1922 with a recurrence and inoperable metastatic lesions. In the course of her examination a chronic lymphangitis of the left arm was recognized. The presumptive primary site was found on the palmar surface of the left hand, where she had had a sore a year before. The epitrochlear node had been involved, and had been incised with prompt healing. The axillary lymph nodes had likewise enlarged and discharged, but were now healing spontaneously. Numerous apple-jelly nodules were, however, demonstrable in the incision scar. The scar of the primary inoculation site contained no tubercles demonstrable by glass pressure, but a biopsy from the epitrochlear scar revealed many, some of them deep in the subcutaneous fat. The patient's condition was so serious as a result of the carcinoma that no further study or treatment was attempted.

It is striking here, as in other cases of this series, and in the literature, that the presence of tuberculous infection was no bar to the healing of the inoculation lesion, the reaction of the subcutaneous tissue being trivial, while that of the lymphatic tissue was much more pronounced.

CASE VIII.—The case of a woman, aged thirty-eight years, seen in 1923, illustrates the years of activity during which a feeder focus may be responsible for a persistent lymphatic involvement, and the relative ineffectiveness of roentgen ray, at least, in the treatment of such primary inoculation sites. The chief complaint was enlargement of lymph nodes on the right side of the neck and beneath the chin, of three years' duration. The onset was marked by the abrupt enlargement and softening of a single node, and subsequent involvement of others, with successive incisions for drainage but without real improvement. A small reddened patch on the right cheek, present for five years, and antedating the lymph node involvement by two years, had been regarded as "lupus" and ignored until recently, when in the belief that it was an epithelioma, roentgen-ray treatment and a small amount of radium had been administered to the point of cutaneous reaction, with the production of atrophy and telangiectasia. The tonsils had been removed two years before the appearance of the adenitis. Pus from the nodes was negative culturally and showed no bacilli of tuberculosis on staining. Under glass pressure, the scar-like "lupus" patch presented little that could be called apple-jelly nodules, so that it was

with some hesitation that its removal with the nodes for diagnosis was advised. It was surprising to find that this supposedly "cured" focus contained, in spite of radiotherapy carried to the point of cutaneous reaction, large numbers of typical tubercles and giant cells, apparently in full activity. The systemic examination revealed no other evidence of tuberculosis, and no good history of contacts could be obtained. The patient did not remain for systemic treatment, but reported subsequently that enlarged lymph nodes had begun to appear under the other side of the chin. It is worth repeating that this lesion (see also Case II) had been treated with roentgen-ray as epithelioma, and not as tuberculosis.

CASE IX.—This patient, a physician in middle life, presented himself with the statement that he had made his own diagnosis on the basis of Case V in this series, which he had watched from the time the diagnosis was made. On examination he presented the same type of pipe-stem lymphangitis in the upper brachial region, visible only on extending the arm above the head (Fig. 4.) An axillary lymph node had softened and in the draining pus, numerous bacilli of tuberculosis had been demonstrated. The primary inoculation focus had been situated on the extensor surface of the forearm, apparently, and had been furuncular in character. Healing had been complete, and although the scar was subsequently completely and deeply excised and serially sectioned no tubercles and only the densest scar tissue could be found. There was no systemic evidence of tuberculosis elsewhere. The lymph nodes were not excised but radium was liberally used, and neoarsphenamin administered, with apparently good results.

This sharp reaction with complete searring and destruction of all organisms at the inoculation site, although not verified by animal inoculation, is apparently what occurred in Case VII. This is theoretically possible, as is found in the tuberculids if the host is sufficiently resistant to destroy all organisms at the point of entry in a furuncular reaction, even though some of them escape to cause trouble in the lymphatic system. Subsequent inoculation of an exposed, healing "boil" seems less likely in view of the absence of tubercles in the scar.

CASE X.—This patient, a healthy girl, aged sixteen years, presented some of the therapeutic problems of this form of tuberculosis of the skin. The inoculation lesion developed on the cheek; the patient thought she had infected a pimple by scratching it. At the time of examination the lesion was an induration with an ulcerative surface and a few scattered puncta, midway between the zygoma and the right labial commissure (Fig. 9). A small bluish nodule over the jaw, and an enlarged lymph node beneath the ramus were

due to metastasis. No history pointing to a source of infection could be obtained, although the patient lived on a farm. Sporotrichosis and extragenital syphilis were carefully eliminated, and a biopsy showed the presence of tubercles in the lesion. The extensive induration (2 cm. in diameter) with the metastatic lesions, would, if treated surgically, involve a gross disfigurement of the face. It was accordingly decided to try the Kromayer lamp with pressure, and to use ultraviolet light (Alpine sun) and arsphenamin conjointly, as systemic treatment. The response was gradual but ultimately very satisfactory. The lesion healed completely (Fig. 10) under repeated severe reactions in the course of four months. The induration disappeared, and the metastatic lesions subsided. Observation of the case terminated before the ultimate result could be determined.

Two cases have also been observed in which the diagnosis of inoculation tuberculosis is not yet proved, although laboratory evidence suggests the tuberculous character of the initial lesion. Both lesions developed at the margin of the umbilicus. In the one which was observed from the start, the patient's first complaint was of pain across the abdomen. An indolent furuncle-like lesion pointed at the upper margin of the umbilicus and discharged, leaving a draining sinus whose appearance suggested a tuberculous origin. Smears from the pus showed acid-fast organisms. Guinea-pig inoculations resulted in varying opinions and an indefinite conclusion, but the lesions simulated tuberculous infection with involvement of lymph nodes and viscera. The general examination of the patient was entirely negative and no signs of a visceral focus could be found. A solitary enlarged node appeared in the right axilla. There was no lymphangitis and the node did not soften. Radium to the umbilicus and the axillary and inguinal lymph nodes, with neoarsphenamin and a general regimen for tuberculosis resulted in a prompt disappearance of symptoms which had, in fact, begun to disappear before the treatment was started. There has been no sign of relapse. A second case had a similar history, but a draining sinus persisted for several months after the initial lesion. There was some disagreement as to the identity of the acid-fast organisms found in the first case, and the tuberculous character of the reactions in animals was again open to question in the first case. These cases, therefore, must be thought of as still *sub judice*.

The importance of differentiating lesions of this type from sporotrichosis, will be apparent to all who are clinically familiar with the two conditions. Fig. 11 illustrates a sporotrichosis of the lip, conforming in every particular to the clinical picture of inoculation tuberculosis except that typical apple-jelly nodules were not recognized. The condition was culturally identified as sporotrichosis. The response of tuberculous and occasionally sporotrichotic lesions

to arsphenamin treatment obscures the differentiation from syphilis, and warns against relying implicitly on therapeutic tests with this drug. This is especially important in cases occurring about the genitalia, as noted by Holt¹⁴ and by Nixon and Short.²⁰ The complete substantiation of a diagnosis of primary inoculation tuberculosis should include the finding of apple-jelly tubercles in the gross lesion, bacilli of tuberculosis in the smear, a negative culture for sporothrix, absence of actinomyces in the pus, positive guinea-pig inoculations of pus and tissue from both primary and secondary lesions, and the demonstration of tubercles in excised tissue from the focus and the lymph nodes. In practice it is difficult to make this chain of evidence complete, but the finding of a focus and presumptive extension to the lymphatic drainage area, with apple-jelly nodules in the primary focus and the histological demonstration of tubercles in excised tissue from both primary and secondary lesions, in the absence of other systemic forms of tuberculosis, makes the diagnosis of primary inoculation tuberculosis reasonably sound.

Summary. The literature is summarized and 10 cases described, of inoculation tuberculosis of the skin with extension to lymph nodes. These cases are equally distributed between the two sexes and in childhood, adolescence and adult life. They suggest that reaction to tuberculous infection and its sequelæ varies with the individual and with circumstances, rather than entirely with previous infection and acquired resistance.

The lesions described as primary are often inconspicuous, may be far from the site of metastatic lymphatic lesions, and are often in old traumatic scars. A history of exposure to tuberculosis may not be obtainable. The apple-jelly nodule, or tubercle in the cutis and subcutaneous fat, is the elementary essential lesion. Its identification by diaseopic pressure is the first aid to a diagnosis.

The primary lesion may be confused with syphilitic chancre, sporotrichosis, actinomyces and epithelioma; the lymphatic metastatic lesions with lymphosarcoma and simple inflammatory bubo.

A painless and indolent lymphangitis may be the only symptom attracting attention in cases primary on the arm, and this may only become visible on the fullest extension of the arm above the head.

A delayed adenopathy, developing after even trifling trauma, should lead to examination of the lymphatic drainage area for a tuberculous inoculation focus.

A primary focus may serve throughout a period of months or years as a feeder to a lymphatic lesion, and be responsible for repeated recurrence of adenitis in spite of drainage, curettage and excision. Scrofulodermatous ulceration of the skin may result at the site of the metastatic lesion.

Roentgen-ray carried to the point of reaction may not destroy the primary focus or retard its feeder activities.

Excision of the primary focus, even if it is only a scar, and of its secondary lymph nodes, is necessary to the best treatment, and should be carried out whenever possible.

In dealing with the focus it is usual to find that the tubercles extend much deeper than might be anticipated, and excision should therefore be carried to the fascia and widely margined.

Radium controls the lymphatic metastatic lesion and is preferable to the roentgen-ray after excision, in the treatment of the excision scars and drainage areas. Large doses, properly screened, should be used, but not carried to excess.

Ultraviolet light from the quartz lamp can be used locally with pressure, in lesions that cannot be excised, and should be employed systemically in the form of general irradiation and artificial heliotherapy.

Moderate doses of neoarsphenamin, which contribute to a good result in cases of tuberculids, and in some cases of tuberculous adenitis, may be used in the treatment of primary inoculation tuberculosis, as part of the general management of the case.

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FURTHER OBSERVATIONS ON THE EPIDEMIOLOGY OF PEMPHIGUS NEONATORUM.

BY RALPH R. MELLON, M.Sc., M.D., P.H.,

AND

DOROTHY W. CALDWELL, M.Sc.,

ROCHESTER, NEW YORK.

(From the Department of Laboratories, Highland Hospital.)

In a recent paper¹ we have directed attention to the possibility that the mother's milk may be a source of infection for infants suffering from the condition known as pemphigus neonatorum or impetigo, as it is sometimes called. We wish to state emphatically that it is not our opinion that these observations have solved the problem of the control of the epidemic form of this disease in institutions; neither would we take the position that the work done so far constitutes final proof that the milk actually *is* a source of infection for the infant.

However, we do take the position that inasmuch as the *Staphylococcus aureus* is at present regarded as the cause of pemphigus neonatorum, the very frequency with which normal milk contains these organisms makes it conceivable that certain strains of them may be virulent and thus assume etiologic importance. Moreover, when all sanitary precautions are aimed to prevent these cocci from reaching the infant, why disregard a source that may yield more of them than is likely to come from all others combined? We trust that this conservative statement of our position will finally counteract the garbled misrepresentation to which the lay press has subjected us.

One of the obstacles that renders conclusions impossible at present has to do with the fact that *Staphylococcus aureus* may be present not only in the normal milk of women whose infants develop pemphigus but often in the milk of those whose infants do not develop it. However, this fact in no way rules out the

possibility we are considering, the great variation in virulence of these organisms being well recognized. The situation is comparable to that existing with suppurative mastitis. Dudgeon and Jewesbury² find that *Staphylococcus aureus* is the most important organism in this condition, yet suppurative mastitis is infrequent in comparison with the number of milks containing *Staphylococcus aureus*.

As regards the presence of *Staphylococcus aureus* in normal milk, the literature as well as our own experience shows the greatest irregularity. Dudgeon and Jewesbury² quote Köstlin,³ who found *Staphylococcus aureus* in 23 per cent of 100 pregnant women, where the so-called albus variety was present in all cases. In 14 cases the secretion was sterile. During the puerperium *Staphylococcus albus* was present in 132 and *Staphylococcus aureus* in 79 and "bacilli" in 22 from 137 cases studied. On the other hand, Cohn and Neumann⁴ isolated *Staphylococcus aureus* only once from the milk of 48 women. This astonishing variation is comparable with our findings at different times. For example, as we reported in the previous paper, from the limited number of controls made from mothers whose babes did not have pemphigus, pigmented cocci were not isolated from any of the cases examined (approximately a dozen); yet more recently during a period of prolonged freedom from the disease, culture of 25 cases showed an incidence of about 30 per cent of aureus in one or both breasts. However, in about half of these cases 0.5 cc of milk yielded only an occasional colony or a few colonies at best, but the other cultures showed the aureus variety as dominant.

The interesting paper by Dudgeon and Jewesbury, although not dealing with impetigo, states that "It is well to realize that infection of the infant from the mother's milk is a greater possibility than has been believed, and that valuable information may be had from the bacteriological and cytological examination of the mother's milk and infant's feces." In their review of the literature of the subject they state that remarkably little work appears to have been done on the subject. Their experience suggests that the organisms present in the milk, such as streptococci, staphylococci and colon bacilli, may at times cause gastrointestinal infection in the infant, particularly however when an actual mastitis exists.

Undoubtedly such organisms, whether pigmented or not, are saprophytic most of the time, but like other microorganisms the staphylococci have cadences of virulence of which impetigo is probably one of the pathologic manifestations. In like manner fusiform bacilli, present in many normal mouths, become virulent at times, and epidemics of such infections result. Such well-known facts should be sufficient answer to any question that might be raised regarding the presence of *Staphylococcus aureus* in milks of

mothers whose babes did not have impetigo. On these grounds an outbreak of infection would be almost wholly a question of virulence, which is not confined to any particular type of aureus.

This point of view is further confirmed by the fact that no serologic or epidemic type of *Staphylococcus aureus* seems peculiar to the disease. It seems likely, though, that pathogenically the infecting cocci have taken on some character that we have not yet learned to recognize. This may be inferred from the character of the pemphigus lesion, which is so often vesicular and leaves a weeping base. This is not the usual lesion caused by staphylococci. That it cannot be entirely explained by the age of the patient is evidenced by the superficial peeling of the fingers of nurses who become infected from the babes.

It was on such grounds that we rigidly isolated the mother of the first child of every outbreak, as detailed in our previous paper. Whether a coincidence or not, the measure was followed by results that were a contrast to those obtained by washing walls and door knobs with bichloride, fumigating rooms, employing extra nurses and so forth. Experience in this hospital seemed to justify the procedure as an addition to the *regular hygienic régime*, even though absolute scientific proof of its soundness is not at hand.

If the laboratory animal could be used as a criterion of virulence for the *Staphylococcus aureus* isolated from this disease the problem would be much simpler, but that it is by no means always possible to make such correlation is generally recognized. This is particularly true when feeding experiments are employed, as evidenced in our previous paper.¹ It appeared also that a culture's invasiveness at different times varies greatly, due presumably to a loss in virulence under the conditions of the laboratory. We are then faced with the problem of the origin of virulence in this rather diverse group of cocci.

Origin of Virulence: Its Relation to Bacterial Variability. When one is confronted with the diversity of types that may be isolated from the individual case perhaps, and certainly from the cases as a whole, it is customary to consider that the organisms have no primary relation to the disease or that the effects they produce are independent of the criteria which we use to separate types. Granting that the latter is probably true, can it not be reconciled first with diversity of type found? And, second, can such diversity itself be explained?

In answer to the latter question the work of Baerthlein⁵ seems pertinent. He isolated four distinct types of staphylococci from one lesion. They included both pigmented and nonpigmented varieties, and were distinguishable by other cultural criteria as well as serologically. After isolating them in purity he showed that experimentally he could derive Types III and IV from Types II and I respectively, while Types I and II are serologically

closely related, even though Type I is an aureus and Type II is nonpigmented.

This diversity of type then is a result of variability within the species. It can no longer be doubted that such changes commonly occur both within and without the animal body. Furthermore, these results have been confirmed in principle by Breinl and Fischer,⁶ whose induced staphylococcus variants are permanently changed as regards their serology and the Gram stain. Is this variation process, which makes for diversity of cultural and morphological type, associated with acquisition of virulence? This question has been affirmatively answered in our own laboratory on more than one occasion.

In a paper given before the American Society of Bacteriologists last December, we showed that from a strain of *Bacillus alkali-genes*, entirely nonvirulent, we were able to derive by variation a strain of moderate virulence as well as one of high virulence.⁷ This character developed suddenly at the time the variants were dissociated, but on continued cultivation under laboratory conditions it gradually disappeared. It is of considerable interest that the strain which developed the higher virulence showed the greatest morphological difference from the other two strains, both of which were coccoid in character; yet serologically two of the strains were identical, while the third showed distinct group and specific immunological relationships. In other words, morphological and serological changes may or may not accompany variability within the species at a time when virulence is acquired.

If under the conditions of the laboratory it can thus be shown that the cyclic conditions which are involved in the biology of bacteria result in the acquisition of virulence, there is no reason why this and the reverse process should not occur in the host tissues as well. As a matter of fact, we know that such do occur. I need only cite the work of Gotschlich⁸ with the plague bacillus which he isolated from a case of the disease. He recovered both a virulent and a nonvirulent type from the same case, and they were culturally quite diverse. Although the avirulent immune serum specifically agglutinated the virulent culture, at a later period the avirulent culture after standing in the icebox for some time spontaneously returned to the virulent type.

Such experimental findings give a plausible explanation why no specific serological type has been identified with impetigo. Furthermore, our serological study of impetigo strains and other staphylococci lend additional support to the position taken. From the standpoint of bacterial genetics it is probable that our specific serological types take origin from ancestral strains possessed of more than one agglutinin. This we showed clearly in our work with *Bacillus alkali-genes*.⁷ This means that if we can isolate such ancestral strains from the host tissue we have, so far as the

bacterium is concerned, the ready potentiality for the disassociation of new types, some of which appear to have increased virulence when first disassociated.

Our serological results with members of the *Staphylococcus* group have revealed clearly the existence of such strains, although the details will be reported at a later time. We have, for example, from a normal breast as well as from the gall bladder two strains of staphylococci which have never shown any pigment but which have been given every chance to do so since their isolation a couple of years ago. Their antisera, however, show that in addition to the white group they also possess antigenically an orange group, which can be absorbed out of their antisera by an orange coccus but which leaves the "white" agglutinin in the serum untouched. On the other hand, this white coccus, which we shall speak of as No. 644, will not agglutinate in the serum of the orange coccus, showing clearly that phylogenetically the latter was in all probability derived from the former. This orange strain was isolated from the skin of a babe having pemphigus and we had several more like it.

It is of note that we isolated four strains from gall bladders which apparently have mixed white and yellow antigenic groupings in them, although the strains themselves are pure-line cultures. In this case the organism was pigmented yellow or orange, yet antigenically it contained "white" receptors which agglutinated with the "white" antibodies in the antiserum of strain No. 644. These latter strains are typified by strain No. 3. We have then strains No. 3 and No. 644, examples of two groups containing mixed agglutinogens, but culturally in No. 644 the white group is dominant, while in No. 3 the yellow group is dominant. Neither strain ferments mannite which is more characteristic of the nonpigmented strains as a whole.

It is clear that the staphylococcus group is serologically fairly heterogeneous, and when one isolates a white coccus he is not sure whether he has a pure type of *Staphylococcus albus* or whether he has a nonpigmented aureus culture or perhaps a mixed strain which includes a pigmented antigen in its grouping. In like manner when one isolates a pigmented staphylococcus he cannot be sure that he has a *Staphylococcus aureus* in pure type, since this organism may contain a very definite agglutinin for purely albus strains. With the background of the experimental work cited, it is entirely possible then to reconcile this serological diversity and the lack of a specific epidemiological type and still regard staphylococci as the pus producers they are really known to be; but it means that the virulence which certain infecting strains may seem to have has probably come about as the result of definite variation which may have involved a loss or an acquisition of pigment-producing capacity.

It is entirely conceivable that a strain of the No. 644 type growing in breast milk could dissociate its aureus component, the variation involving perhaps acquisition of virulence. In fact, certain of Baerthlein's transformations⁵ with these cocci were brought about in litmus milk. The evidence is constantly increasing that these cyclic fluctuations take place with the bacteria as a part of their natural life history, and although most of the variants among such groups are probably saprophytic, the variation change *may* include the development of virulence.

Although throwing no light on the nature of virulence itself, such a conception of its origin aligns it with processes that we believe are periodically occurring with all groups of microorganisms. Fundamentally they are of an adaptive nature to preserve the life of the strain itself. The general subject of microbic heredity and the biology of bacteria has been a central interest of this laboratory for many years, and to those interested we may refer the reader to the publications indicated in the bibliography.^{9, 10, 11, 12, 13}

Conclusions. 1. Normally human milk usually contains nonpigmented staphylococci and a varying percentage contain pigmented staphylococci.

2. The fact that *Staphylococcus aureus* is the probable cause of pemphigus neonatorum opens the possibility that the milk may in certain instances be a source of such infection, namely, when the cocci they contain are virulent for the infant.

3. It is not contended that the observations so far made are sufficient to establish human milk as a source of such infection.

4. There are ample experimental grounds for the view that the heterogeneity of the staphylococci is the direct result of variability, which is at times associated with the sudden appearance of virulence.

5. This point of view, together with the lack of any epidemiological type for the disease, makes staphylococci *from any source* potential causes of outbreaks of pemphigus neonatorum.

6. It is on such grounds that segregation of those mothers, who have been tentatively regarded as carrying staphylococci virulent for infants, has been employed.

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NYSTAGMUS: NEURO-OTOLOGIC STUDIES CONCERNING ITS SEAT OF ORIGIN.*

BY I. LEON MEYERS, M.D.,

ATTENDING NEUROLOGIST, LOS ANGELES GENERAL HOSPITAL, LOS ANGELES, CALIF.

(From the Neurologic Service, Los Angeles General Hospital.)

NYSTAGMUS is a phenomenon consisting of a series of rhythmic, biphasic movements of the eyes, the eyes in the first phase deviating from their position of rest or fixation and in the second phase returning to (or near) their original position. The movement in the first phase is carried out slowly and is, accordingly, designated as the slow component; that of the second phase is rapid and jerky in character, and is known as the quick component. The latter being the more conspicuous of the two phases is the one that is employed to indicate the direction of the nystagmus, so that the term "nystagmus to the right" indicates a primary deviation of the eyes to the left which is followed by a return jerk to the right, and so forth.

The phenomenon, leaving out of consideration here the nystagmus caused by visual disturbance, such as is seen in degenerative disease of the choroid and retina, as in miner's nystagmus, in which case the rhythmic movements of the eyes are rather pendular in type, is the motor manifestation of an excitatory process in the vestibular system, either at its periphery in the labyrinth, or along the course of the vestibular nerve as far up as its termination at the nucleus Deiters' and nucleus Bechterew in the pons and the nuclei tecti of the cerebellum.¹ It is not, as yet, definitely known whether excitation of the secondary afferent neurone in this system, the

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neurone which, originating at these nuclei, ascends to the mid-brain as the vestibulomesencephalic tracts, is also associated with nystagmus. Experimental evidence tends to show that excitation of these tracts produces only conjugate deviation of eyes and its allied phenomena, such as rolling movements or falling to one side.² The excitation may be produced artificially as when nystagmus is brought about by the rotation or caloric testa of Bárány; it may be caused by irritation of the labyrinth or nerve by neoplasms, inflammatory exudates or by trauma; and it may, finally, be the result of the unantagonized activity of the intact vestibular system which results from the destruction of this system on one side, as in section of the 8th nerve on one side, in which case the nystagmus is invariably toward the normal side.

The motor manifestation resulting from such excitation of the vestibular system is not, however, always biphasic. In the lower vertebrates, as in the petromyzon, in the turtle, or the frog, it is limited to a slow deviation of the eyes which persist in their new position showing no tendency to a return jerk. This type of a reaction may be observed also in man under a moderate degree of narcosis. Deep narcosis on the other hand, when this is so profound as to suppress the corneal reflex, abolishes alike the slow as well as the quick component. These observations have led to the conclusion that the slow component is phylogenetically and ontogenetically the more primitive and elementary motor reaction, that it is consequently the more resistant of the two, and that its seat of origin is at the lower motor nuclei in the pons and midbrain (the nucleus abducens in the pons and through the medium of connecting fibers in the posterior longitudinal bundle in the contralateral nucleus oculomotorius).²

As to the seat of origin of the quick component it is still a moot question. Bárány believed that this component forms a part of a composite reflex which originates in its entirety in a nystagmus center which is situated, according to him, in the cerebellum.³ Bartels⁴ studying the question experimentally, concluded that the rapid phase originates in the cerebrum. This view was opposed by Bauer and Leidler⁵ who from their experimental studies concluded that neither phase of the nystagmus is disturbed by the destruction of the cerebrum even when the destruction is so extensive as to include the optic thalami and adjacent structures as far down as the corpora quadrigemina.

Wilson and Pike,⁶ experimenting on dogs and cats, found that the quick phase is abolished by the complete removal of the cerebrum provided such removal includes the optic thalami. A. C. Ivy⁷ who carried out a series of experiments on pigeons, rabbits, cats, pups and dogs concluded that the quick phase of nystagmus is not dependent upon the integrity of the cerebrum but is determined entirely by some center below the thalamus.

Neuro-otologic Studies in Man. In an endeavor to determine this question I carried out a series of neuro-otologic studies in cases of apoplexy with hemiplegia which had as one of their symptoms conjugate deviation of the head and eyes or of the eyes alone. As it is well known, conjugate deviation of the head and eyes, or of the eyes alone, in which the eyes are directed away from the paralyzed side, in the words of Vulpian, "the patient looking at his lesion" is a phenomenon which is very common in cases of hemiplegia when these are of vascular origin. It is absent only in lesions that either are very mild or are so severe as to interfere with the activity of the intact hemisphere. The symptom is to be ascribed to the destruction of that part of the cortex cerebri, or of its fiber tracts in the internal capsule, which controls rotation of the head and eyes or of the eyes alone toward the opposite side of the body. This laterogyric action of the head and eyes may be brought about, experimental evidence shows, by stimulation of one of two regions in each hemisphere, namely, an area which is situated in the pre-Rolandic or motor zone, more specifically, in accordance with the researches of Beevor and Horsley in the orang,⁸ in the middle and inferior frontal convolutions of the frontal lobe; and another area which is situated in the sensory zone, or more specifically, in accordance with the studies of Luciani and others,⁹ in the angular gyrus of the parietal lobe. The abolition of this function from one hemisphere allows, it may be assumed, the laterogyric action of the other hemisphere to come into play unantagonized and unhindered, producing in this manner a rotation of the head and eyes toward the side of the lesion. The symptom is generally pronounced for a day or two following the stroke. It then becomes progressively attenuated so that after a week or ten days it is hardly noticeable. It frequently may be detected, however, even then by the slight resistance of the patient to passive rotation of his head toward the side of the paralysis, or by his reluctance to look in that direction. This latter condition may last for five to seven days when finally either through recession of the early inflammatory reaction and the restitution of the functional integrity of the affected fibers or as a result of a compensatory action by other parts of the cerebrum, such as is presumably at play in the recession of aphasia all trace of the phenomenon is lost.

Labyrinthine stimulation during this period of conjugate deviation of the eyes when the laterogyric action of the affected hemisphere of the cerebrum is definitely in abeyance, should, I thought, accentuate the already existing deviation of the eyes but produce no rapid phase to the side opposite to the lesion, whenever the stimulation is such as would produce normally a nystagmus to the corresponding side, if the rapid phase has its origin in the motor area of the cerebrum. It should produce then no rapid phase to the side of the intact hemisphere, as well as no slow, primary deviation

towards this side, in the case such stimulation would produce normally a nystagmus to the side of the affected hemisphere, if both these phases are, like the abdominal and cremasteric reflexes, dependent upon the functional integrity of this area. It should finally, produce a normal, biphasic reaction, if both phases originate at the nuclei of the eye muscles in the midbrain and pons and are, like the pupillary reaction to light, or the corneal reflex, independent of the cerebrum.

I have accordingly studied by the caloric tests of Bárány (warm as well as cold irrigations of the ears) 16 cases of hemiplegia, with conjugate deviation of the eyes, for a variable time following the stroke.

The results of these studies are shown in the following illustrative cases:

Case Reports. CASE I.—Mrs. A. McC. (Los Angeles General Hospital, No. 19075); right sided hemiplegia of vascular origin, with both sensory and motor aphasia, conjugate deviation of eyes to the left. The patient became suddenly paralyzed in the right side of the body (lower part of the face, arm and leg) at about 6.00 A.M., January 14, 1924. She became partly unconscious then and remained in same condition until about 10.00 A.M. When examined at about 11.30 A.M. patient was fully conscious, but could not understand the simplest questions or commands, nor could she utter a word. Her pupils were unequal, the left wider. Both reacted to light. The tendon reflexes in the right arm and leg were hyperactive. The abdominal reflexes on the right side were absent. Babinski on that side but no ankle clonus. Sensation seemed to be preserved. Patient had conjugate deviation of the eyes to the left but was able to move them now and then spontaneously to the right.

Otologic Examination (this patient and two others have been examined by the author in association with Dr. Isaac H. Jones). Patient, as far as could be learned from her family, never had any ear trouble. On douching her right ear with water at 68° F. and head at 60 degrees back, the eyes after twenty seconds were drawn to the right, and there occurred a horizontal nystagmus to the left. The nystagmus had kept up for about five minutes. It was normal in rhythm and amplitude. On douching the left ear with water at 68° F., head at 60 degrees back, the eyes after twenty seconds were drawn to the extreme left angle, where they manifested a tendency toward slight nystagmus to the right. This stopped after a few moments, and in spite of prolonged douching there was no further disturbance in either eye. It was thus obvious that the motor action responsible for the quick component was either absent or, when present, was so feeble as to be incapable of moving the eyes out from the left angle. Patient exhibited no constitutional

response-pallor, sweating and nausea, although one ear was douched after the other, and the douching was kept up for a long time.

On the day following (January 15) patient's condition was much worse. When examined about 5.00 P.M., she was deeply in coma and there was no vestibular response attainable from irrigating either ear. (This patient was examined in the presence of Prof. Georges Portman, professor of otology at the University of Bordeaux, who visited Los Angeles at that time). Results identical with the foregoing—a slow component only on irrigating with cold water the ear on the side of the lesion and a more or less normal nystagmus on irrigating the ear on the opposite side (the side of paralysis) whenever this irrigation was done while the patient was conscious, and no response of any kind and from either ear if the patient during such procedure was deeply unconscious, have been obtained in all the cases so far studied. The results obtained in the patients when conscious thus show that a lesion of the laterogyrie center or its conducting tracts in the internal capsula on one side, as manifested by conjugate deviation of the eyes to the side of the lesion, abolishes the quick component of nystagmus to the other side. It shows further that such a lesion does not affect, apparently, the slow component of nystagmus. This last statement may have to be modified with the further study of the phenomenon. I have gained the impression from my observation in the cases so far studied that the slow component is, to some extent, also modified by such a cerebral lesion. This component, or the primary deviation of the eyes toward the intact hemisphere which follows the cold irrigation of the ear on the corresponding side has been frequently observed to be of much smaller range than normal, and the quick component to set in before the eyes have reached the midline.

Patient died on January 30, 1924. The necropsy performed by Dr. George Maner showed the following: The pia over the whole of both hemispheres is edematous and cloudy, but thin; the convolutions are slightly atrophied and the vessels over the left hemispheres are collapsed and empty. The left middle cerebral artery just at its formation is filled with an adherent soft grayish-red thrombus. The remainder of vessels are collapsed. The lateral ventricles are symmetrical, not dilated. On section the gray matter of the optic thalamus and the corpus striatum of the left side is of a pale, dirty gray-brown appearance and of softened consistency as compared with the same area on the other side. The white matter in the internal capsule on the left side is softened and friable. Practically the whole of the brain substance of the left cerebral hemisphere is somewhat softened. Right side showed no involvement. Cerebellum, pons and medulla do not appear to be altered.

CASE II.—A. C. (Los Angeles General Hospital, No. 203698) Left-sided hemiplegia of the capsular type with slight involvement also of the right side. The rapid phase of nystagmus is practically absent on irrigating with cold water the right ear; it has a tendency to be atypical on irrigating the left ear. (This patient, it will be noted, was examined while he was unconscious.)

A male patient, aged sixty-nine years, an American, had a stroke of apoplexy with unconsciousness at about 6.00 A.M. of February 15, 1924. When examined at about 7.00 P.M. of that day patient was still unconscious. He did not utter a sound or respond to commands. He moved his right arm now and then, but none of his other limbs. The left arm and both lower limbs were definitely atonic. The tendon reflexes could not be obtained in any of these. The Babinski was positive and the cremasteric and abdominal absent on both sides. His pupils were rather small but equal and reacted promptly to light. Blood pressure was 172/115. He had a conjugate deviation of the head and eyes to the right. The eyes moved, however, now and then spontaneously toward the left as far as the midline.

Otologic Examination (in association with Dr. H. F. Linthicum). Drum membrane is intact on both sides. Douching the left ear with water at 68° F. and the head 60 degrees back, produced after about twenty seconds, conjugate deviation of the eyes to the left which was followed by indefinite rolling and jerky movements to the right but no definite type of nystagmus. On repeating the irrigation of the same ear about a half hour later there set in after twenty seconds a conjugate deviation of the eyes to the left which was followed by a definite rhythmic slow nystagmus of a large amplitude and horizontal in type to the right. This was interrupted occasionally by the eyes going into conjugate deviation to the right again. The nystagmus was marked for about a minute; it then became slow and indefinite and remained so for about three minutes. On douching the right ear with water at 68° F. and head 60 degrees back, there occurred, after about twenty seconds, an accentuated conjugate deviation of the eyes to the right; this was followed by indefinite, irregular, intermittent, small, horizontal and rotatory nystagmoid movements which formed a marked contrast to the large, slow and rhythmic nystagmus obtained from the left side. The duration of this reaction was about a half a minute. Despite prolonged douching there was no nausea, vomiting or pallor. Patient's unconsciousness gradually deepened and he died about thirty-six hours later. A permit for an autopsy was refused.

In contrast to the foregoing two cases in which the cerebral lesion was extensive was the following case in which, from the clinical course it may be assumed that the lesion was limited to the pre-Rolandic or motor zone of one hemisphere.

CASE III.—C. D. (Los Angeles Hospital, No. 206314). Right-sided hemiplegia with Broca's aphasia (anarthria of Marie); conjugate deviation of the eyes to the left.

A male patient, an American, aged forty-seven years, was admitted to the hospital in a stuporous condition about 6.00 P.M. of March 28, 1924. No history of onset. When examined at about 10.00 A.M. of March 31, 1924, the patient was fully conscious. He had motor aphasia (or Marie's anarthria) which was complete, as he could neither speak spontaneously nor could he repeat words spoken to him, but his comprehension of speech was unusually good. He presented a paralysis of the lower part of the face, arm and leg on the right side. Pupils were equal and reacted promptly to light and accommodation. No difficulty of deglutition. Tongue deviated to the right. Tendon reflexes in the right limbs were hyperactive. He had a Babinski, Chaddock and a Gordon on the right side, but no ankle clonus. The cremasteric and abdominals were lost on that side. All the reflexes were normal on the left side. General sensibility seemed to have been preserved everywhere. He appeared to have had no hemianopsia. He showed a tendency to conjugate deviation of the eyes to the left, but was well able to move his eyes to the right.

Otologic Examination (this and the remaining 11 cases have been studied by the author in association with Drs. Homer S. Keyes and J. M. Neilson, resident physicians at the Los Angeles General Hospital). Drum membrane is intact on both sides. Irrigating the right ear with water at 68° F. and head 60 degrees back, produced after twenty second a conjugate swing of the eyes to the right which at the time they reached the midline and before entering the right half of the eyes, began to show a nystagmus to the left, the rapid phase, which was horizontal in type, rhythmically pulling the eyes into the left canthus. This lasted for about three minutes. On placing the patient in an upright position, with head 30 degrees forward, the nystagmus becomes rotatory in character but continued to be to the left (the normal reaction for this position). The constitutional response following the irrigation was very severe. On irrigating the left ear with water at 68° F. head 60 degrees back, there set in after about twenty seconds an increase in the pre-existing conjugate deviation of the eyes to the left. This was followed by a few oscillatory movements to the right which quickly ceased, the eyes remaining in a position of deviation to the left, although the irrigation was kept up for nearly five minutes. On placing the patient upright with the head 30 degrees forward, the eyes continued to stay in this position. During the irrigation of this ear a tendency was noted on the part of the eyes to become dissociated in their direction of fixation, the homolateral eye remaining deviated in the left and the right eye moving toward the right and remaining near the midline. This dissociation in the position

of the eyes while irrigating with cold water the ear on the side of the lesion was noted in a number of instances. It suggests the possibility that in the laterogyric action of the eyes each hemisphere innervates more powerfully the contralateral eye, hence this persistent deviation in above quoted case of the left eye to the left, than the homolateral eye which showed a tendency to move to the right. The constitutional response following the irrigation of the left ear was distinctly subnormal. The patient was reexamined on April 2 and again on April 5. He was able then to move his eyes voluntarily in all directions, but when at rest, the eyes tended to become conjugately deviated to the left. His general condition showed considerable improvement. He was quite alert and coöperated in his examination with intelligence. He was able to speak a few simple words although he mispronounced them. The otologic studies on either of these dates gave results which were in all respects identical with those obtained on March 31. He was reexamined on April 14 and again on April 16. On these dates he showed no conjugate deviation of the eyes but when asked to look to the right he showed a tendency to turn his head in that direction instead of turning his eyes that way. His general condition was then very good. He walked around with comparative ease and while dysarthric was able to express his wants in sentences. The otologic examination showed that there was still a striking difference between the nystagmus obtained on caloric stimulation of the right labyrinth and that obtained from the left. The nystagmus obtained on the cold irrigation of the left ear, was oscillatory and pendular in character and its duration was short, whereas that obtained in the same manner from the right ear, while frequently modified, was more or less of the normal type. This difference has, moreover, been noted in several instances as late as three months following the apoplectic stroke, a fact of much practical importance. The physician in carrying out the labyrinthine tests on a patient with a hemiplegia of recent onset in an endeavor to determine the condition of the vestibular system should bear this fact in mind, as on an impaired nystagmus to the side of the paralysis obtained in such a patient may be due entirely to the cerebral lesion and in the absence of any trouble whatever in the labyrinthine mechanism.

The impairment of the nystagmus caused by the cerebral lesion is not, however, it appears from the studies I have so far made, a permanent phenomenon. It tends to recede, and in about six months following the stroke practically no difference is to be detected in the phenomenon as obtained from either labyrinth.

ADDENDUM.

I recently had an opportunity to study the vestibular responses in a case of unilateral convulsions with conjugate deviation of the

head and eyes—a condition which represents the direct opposite to that of apoplexy with hemiplegia. The report follows:

CASE IV.—(No. 221992). A male patient, aged thirty-four years, with taboparesis, was admitted to the psychopathie department of the Los Angeles General Hospital, on January 16, 1925. I examined him in association with Drs. Eshman, Calvert and Sugar, resident physicians at the hospital, at about 6.30 P.M. of January 22, 1925. He was then in coma and had convulsions of the clonic type which involved the leg, arm, and face on his right side. His head and eyes were turned to the right, in the direction opposite to the hyperactive motor cortex of the cerebrum. His eyes moved, however, spontaneously now and then to the left. The patient, it was reported, had never had any ear trouble. Labyrinthine stimulation, while he was in this state, by the cold caloric to the right ear produced an accentuated conjugate deviation of the eyes toward the right but no rapid movement toward the left. Stimulation of the labyrinth by the cold caloric to the left ear gave rise, on the other hand, to a normal, biphasic reaction toward the right. The nystagmus so obtained from this ear was of large amplitude, horizontal in direction (the irrigation having been done with the patient in the recumbent position with his head at 60 degrees back) and lasted for a minute following the cessation of irrigation, (two and a half minutes).

I reexamined him on February 22, 1925. He walked around then in a normal manner and was fairly clear mentally. Neurologic examination showed the following:

Argyll-Robertson pupils. Ocular movements normal. No spontaneous nystagmus. Fundi were normal. Speech was tremulous, parietic. Deep reflexes in arms and legs lost. Cremasteric and abdominal reflexes were present on both sides. No Babinski on either side. Hearing was excellent in both ears.

On stimulating his labyrinths with cold water a rhythmic, biphasic reaction, the rapid phase of which was toward the side opposite to the ear irrigated, was obtained from either side. The amplitude of the nystagmus so obtained from the left ear (from the side corresponding to that of the hyperexcitable and hyperactive motor cortex) was, however, much greater than that of the nystagmus from the right ear.

There was similarly a great difference between the pastpointing reactions from the two sides. Whereas on irrigating the right ear the initial range of the pastpointing by the right arm to the right was 3 inches, that of the left arm to the left on irrigating the left ear was 12 inches.

The reactions on stimulation of either labyrinth were obtained from the horizontal canals only (when the head of the patient was at 60 degrees back), no response having been obtained from the vertical canals (when the head was at 30 degrees forward).

Conclusions. 1. In cerebral hemiplegia of vascular origin during the period of conjugate deviation of the eyes to the side of the lesion it appears to be impossible to evoke nystagmus to the side opposite to the lesion. Labyrinthine stimulation of a character which evokes this reaction to the corresponding side in a normal person produces instead—provided the patient is not deeply unconscious, a persisting and frequently intensified conjugate deviation of the eye to the side of the lesion.

2. The substitution in this condition of nystagmus by conjugate deviation of the eye to the side of the lesion, or merely an impairment of the nystagmus, may outlast by months the conjugate deviation of the eyes which as an initial phenomena was brought about directly by the cerebral lesion, a fact to be remembered in evaluating the atypical nystagmus resulting from stimulation of the labyrinth in patients with a recent hemiplegia.

3. The motor impulse for the rapid phase of nystagmus originates in the cerebrum. The fact that it was found to be abolished by lesions which gave rise to hemiplegia with pure motor aphasia, and no phenomena referable to the sensory cortex or optic thalamus makes it highly probable that it has its origin in the laterogyric center of the eyes, which is situated, in accordance with the researches of Beevor and Horsley, in the middle and inferior frontal convolutions, in an area adjacent to the speech center of Broca. The corpus striatum undoubtedly play a part in the production of this phenomenon. In a case which I reported in a previous publication¹⁰ and in which microscopic study of the brain showed degeneration of the globus pallidus and no lesion of the motor cortex, pyramidal tracts, optic thalamus, midbrain or pons, labyrinthine stimulation produced a nystagmus which was normal in direction and amplitude but greatly lessened in duration, the eyes showing a tendency to persist in the primary phase of the nystagmus—the conjugate deviation.

4. The motor impulse for the slow phase of nystagmus originates, most probably, in the nuclei of the eye muscles in the midbrain and pons. It may be produced by appropriate stimulation of the labyrinth to either side, regardless of the cerebral lesion. It appears highly probable however, that this phase is to some extent also influenced by cerebral activity.

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REVIEWS.

WILLIAM CRAWFORD GORGAS: HIS LIFE AND WORK. By MARIE D. GORGAS and BURTON J. HENDRICK. Pp. 359; 10 illustrations. Philadelphia and New York: Lea & Febiger, 1925. Price \$5.00.

WITHOUT doubt the greatest feat that American medicine has yet achieved is the discovery of the cause and method of transmission of yellow fever and its extermination in this continent. Equally without doubt General Gorgas is the one individual to whom chief credit is due for the achievement of the last-named feat. In fact if it had not been for Gorgas' invincible determination to apply Reed's discovery, in spite of all obstacles, the authors assure us that the latter might long have remained an unfruitful academic achievement. It has become a truism to state that control of the stegomyia alone made possible the building of the Panama Canal and yet this epochal event was only the dramatic first fruit of labor which Gorgas hoped (and not without reason) would soon eradicate this former scourge from the globe.

The lack of shadow contrast in the tale is pardoned by the reader in return for the exalted enthusiasm which sweeps through the book; and if other actors in the most important scene of the play have not quite received their due, there is glory enough for all and their turn will come later if it has not already been recorded elsewhere.

The life history of this "ragged, barefoot little rebel" from Baltimore, who so accomplished his inspired duty that "his name will shine for ages in the history of our race," is most attractively told by the one best qualified to know, working with one of the best biographers of our day. And the results are all that one might hope for. One finishes the volume only too quickly, and is at a loss whether to admire more the winning personality of the man or the sterling qualities of the administrative genius. Surely if contemplating the lives of eminent contemporaries is one of the surest sources of inspiration, this volume should be read by every student of medicine—graduate and undergraduate. E. K.

DIABETIC DIET. A HANDBOOK FOR DIABETICS. By A. DORIS MCHENRY, B.A., and MARJORIE M. COOPER, B.A. Pp. 62. New York and London: Harper and Brothers, 1925.

THIS little book is recommended chiefly by a goodly number of recipes that will be found valuable in constructing and varying the

diabetic's diet. In addition there are brief chapters on the composition and value of food, methods of urinalysis, weights and measures, and the general plan of diabetic diets with sample menus. The sample diets as given are open to some criticism. Too great a percentage of carbohydrate is given in the form of fruit or milk sugar. Thus in a very restricted diet containing only 30 grams of carbohydrate, two-thirds of this is given in the form of orange, grapefruit and milk. In another diet containing 98 grams of carbohydrate, no 15 or 20 per cent starch-containing vegetables are used but whole wheat bread and apples are included. R. K.

PHYSICAL DIAGNOSIS. By W. D. ROSE, M.D., Lecturer on Physical Diagnosis and Associate Professor of Medicine, University of Arkansas. Fourth edition. Pp. 755, 319 illustrations. St. Louis: C. V. Mosby Company, 1924.

In the fourth revised edition of this work the author has continued in his original purpose to write a text for the student and general practitioner. This he has done quite successfully. Physical examination of thorax and abdomen are well and completely covered. A few minor details might be criticized. For instance, auricular fibrillation is still described as an unsystematized fibrillary twitching of the auricular muscle and no mention is made of the fairly well established views in regard to circus movement in this condition. In describing the physical signs of massive pulmonary collapse no mention is made of the displacement of mediastinal structures. In the main the treatment of the subject is adequate. The chapter on Examination of the Nervous System is not full enough. The book is profusely illustrated; some of the illustrations are good but many of them are rather poor, due to the quality of paper rather than poor photography. R. K.

COMMON INFECTIONS OF THE FEMALE URETHRA AND CERVIX. By FRANK KIDD, M.A., M.Ch. (CANTAB.), F.R.C.S.(ENG.) And A. MALCOLM SIMPSON, B.A., M.B., D.P.H. (CANTAB.). With additional chapters by GEORGE T. WESTERN, M. D., and M. S. MAYOU, F.R.C.S. Pp. 183: 9 illustrations. London: Humphrey Milford, Oxford University Press, 1924.

THE reviewer feels the authors have indeed achieved the main objective of the book, namely, the description of simple methods of treatment of gonococcal and other infections of the female urethra

and cervix which will be within the scope of the general practitioner to apply, for it is to general practitioners that the majority of such cases will present themselves. The book is well planned and well written. It is based upon clinical observations made since 1917 in a new department of the London Hospital. The descriptions of various infections are concise, the methods of treatment are detailed, and the additional chapters by the co-authors are excellent supplementary resumes of bacteriology and ophthalmia. While perhaps intrauterine medication in acute pelvic inflammatory disease may not be accepted in America, yet the findings of the authors seem to show its merit. One is surprised at the omission of any reference to the tracheloplastic operation of Sturmdorf for chronic endocervicitis.

P. W.

GYNECOLOGY, MEDICAL AND SURGICAL. By P. BROOKE BLAND, M.D., Assistant Professor of Gynecology, Jefferson Medical College; Assistant Gynecologist, Jefferson Medical College Hospital; Gynecologist, St. Joseph's Hospital. Pp. 1257: 644 illustrations. Philadelphia: F. A. Davis Company, 1924.

THE volume in hand, the Students Edition, is bulky and heavy, and one is pleased to learn that another edition, the Library Edition, is published in two volumes, presumably more easily handled. In presenting this compilation, the author frankly states in the preface that there is no claim to anything especially new, to which the reviewer agrees. That a scarcity of books upon this subject could have been responsible for the production of this work is to be doubted, for several excellent works are referred to in the preface.

The subject matter follows the arrangement of Dr. Montgomery's well-known textbook, morbid conditions being classified pathologically rather than anatomically, and the text is quite well up with the most recent of the ever-changing opinions and literature in gynecology. Many of the illustrations are excellent, some are poor. A certain sense of disproportion is felt here and there, as witness the seven pages devoted to the details of the Wassermann reaction compared to a scant page or more on the treatment of sterility.

P. W.

AN INTRODUCTION TO DERMATOLOGY. By SIR NORMAN WALKER. Eighth edition. Pp. 373; 92 plates and 80 illustrations. New York: William Wood & Co., 1925.

THE author makes no pretense at presenting a complete system, and for the purpose intended, namely a text for students, his book

is a success. The refreshingly direct, rugged style of the author must at once influence the dermatologist in favor of some of the radical positions that he frequently takes. Thus, the subject of eczema finds no place in the book; it has gone by the board in keeping with the ideas of Highman, in this country, and others. "Dermatitis" takes its place. As to the illustrations, many are so excellent that it is hard to understand how the author could admit so many poor ones. This applies to the colored plates as well as to the other illustrations.

On the whole, the book surpasses many American ones as a teaching medium for students, but it cannot rank with them in value to the dermatologist or general practitioner.

F. W.

SELECTED MEDICAL PAPERS OF ALFRED WORCESTER. Pp. 339, 7 illustrations. Boston: The Four Seas Company, 1925.

THE eighteen articles reprinted in this book were published as a surprise to Dr. Worcester, in order "not only to pay a just tribute to a great physician and give pleasure to Dr. Worcester's friends, but to put in available material which will be of assistance to . . . historians."

E. K.

THE TREATMENT OF FRACTURES IN GENERAL PRACTICE. By C. MAX PAGE and W. ROWLEY BRISTOW., St. Thomas's Hospital, London, England. Pp. 235; 141 illustrations. New York: Oxford Medical Publications, American Branch, 1923.

THE aim of this book is to present to the working medical profession a small, handy volume that deals simply and clearly with the practical side of the treatment of fractures. It takes up the question of, first, the diagnosis, the repair, the complications and the general principles. Subsequent chapters consider in detail the separate fractures that are met with in the human subject. The most modern ideas in the treatment of fractures are well presented and also well illustrated.

Since the general public has become more critical of the terminal results in fractures and have at their disposal the roentgen ray to show poor or good position, the practitioner at large must have a good working knowledge of fractures. This little book gives all that the average case of fracture requires. It is of handy size, its thought well expressed and the subject matter presented in an agreeable style.

E. L.

LA SIFILIDE IGNORATA E STRANA. By PROF. CARLO MARTELLI, Docente di Anatomia Patologica e Clinica Medica nella Università di Napoli, Socio della R. Accademia Medico-Chirurgica. Second edition. Pp. 642; 73 illustrations. Napoli: Casa Editrice Libreria von Idelson, 1923.

WHILE this volume on unsuspected and atypical syphilis will naturally not have a wide demand in this country, nevertheless its merits are such that it should be available to anyone wishing to look into the subject more thoroughly than is possible in textbooks on syphilis. In the first third of the book, are discussed general biological and clinical considerations on syphilis as a whole; in the second third, the clinic of 14 types of unsuspected or atypical syphilis (febrile syndromes, cardiovascular syndromes and so forth); and in the last third, their diagnosis, prognosis and therapeutics. A bibliography of 50 pages adds to its value to students of all nationalities.

E. K.

SERUM DIAGNOSIS OF SYPHILIS BY PRECIPITATION. By R. L. KAHN, M.S., Sc.D., Immunologist, Bureau of Laboratories, Michigan Department of Health. Pp. 237; 3 plates; 55 tables. Baltimore: Williams & Wilkins Co., 1925.

THIS volume records the experiments conducted during the past three years by the author on the precipitation phenomenon in syphilitic serum, and presents the details of the development, the standardization and the clinical applications of the Kahn test. The greater part of the material included has appeared from time to time in the author's publications, but its presentation in this book enables the reader to correlate the various procedures and to get a better grasp of the significance of the test. The book gives one an idea of the enormous amount of work performed in the development and standardization of this test. Underlying theories are discussed only insofar as they have practical applications. Special attention is given to the necessity for observing strict precautions in the preparation of the antigen and rigid observance of the technique in order that consistent results may be obtained in different hands. The parallelism between this precipitation test and the Wassermann test in the author's laboratory is well demonstrated.

The book is of interest primarily to serologists, and secondarily to those engaged in the study of the effects of the different procedures in the application of specific chemotherapy in the treatment of syphilis.

J. S.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE.

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI.

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Notes on the Therapeutic Value of Pneumococcus Antibody Solution Subcutaneously Administered in Lobar Pneumonia.—In view of the fairly extensive use of Huntoon's antibody solution in the treatment of pneumonia, the report of OLIVER and STOLLER (*Arch. Int. Med.*, 1925, 35, 266) will prove of interest. They obtained the following results in a series of 23 patients to whom the solution was given subcutaneously: A low incidence of thermal reactions; a painful tissue reaction, persisting at times for days; a subjective and objective improvement in 4 cases and no benefit in 19 cases; failure to sterilize the blood; inferiority of the antibody solution as contrasted with pneumococcus antiserum in Type I pneumococcus infection; failure to prevent extension of the pneumonic process from one lobe to another; and a benefit in Type IV pneumococcus pneumonias as compared to the control cases. Additional results from the use of this solution should be published by other observers, as it is only from a study of statistics in the mass that the results of a therapeutic procedure of such promise may be properly evaluated.

Pancreatic Enzymes in Cholecystitis.—G. M. PIERSOL and H. L. BOCKUS (*Arch. Int. Med.*, 1925, 35, 204) employ the method of Einhorn in estimating the pancreatic enzymes in cases of cholecystitis. They claim that this is a simple quantitative method probably as accurate

as any so far devised. It would seem from a study of their results and their tables that the method can hardly be called truly accurate and the impression must not be given that the method or their results are in any sense specific but rather simply additional data which are of use in evaluating the other signs and symptoms of gall bladder infection. They found that a definite reduction in the amount of pancreatic enzymes is additional corroborative evidence in favor of cholecystitis. The average amount of reduction of the enzymes was over 50 per cent in 85 per cent of their 40 cases of cholecystitis.

Contributions to the Pathology of Experimental Virus Encephalitis.
II. Herpetic Strains of Encephalitogenic Virus.—S. FLEXNER and H. L. AMOSS (*Jour. Exper. Med.*, 1925, 41, 233) have had the opportunity of working with the Levaditi strain of herpetic-encephalitic virus. They have contrasted its action with that of a pure strain of herpes virus which they have called the H. F. strain. They find that this strain is highly encephalitogenic. This is, in their opinion, of great theoretical and practical importance. The fact that such a strain exists, which is even more irritating to the central nervous system than that of the Levaditi strain, would tend to show that the criteria upon which Levaditi advocates this strain as the cause of lethargic encephalitis are not sufficiently exact to warrant his assumption. Flexner and Amoss feel that this is a virus which is probably herpetic in origin. They maintain that there exist weaker and stronger strains of virus which are probably always herpetic in origin and that it is undoubtedly the stronger strains which have been isolated in reported cases of epidemic encephalitis and which are not the true cause of the disease. Epidemic encephalitis is associated accidentally with this group of viruses at times and they bear no casual relation to the disease.

All-day-blood-sugar Curves in Nondiabetic Individuals and in Diabetic Patients with and without Insulin.—One of the difficulties in the use of insulin has been to space satisfactorily the doses of insulin. The present paper by JONAS, MILLER and TELLER (*Arch. Int. Med.*, 1925, 35, 289) reports a series of 34 blood-sugar-concentration curves made in periods up to twenty-four hours. Their results are so valuable and put so succinctly that they are worth quoting at least in part. "A series of 34 blood-sugar-concentration curves were made on 29 patients, 6 nondiabetic and 23 diabetic, and covered periods up to twenty-four hours. This was done in an effort to work out a more satisfactory routine method of regulating the dosage and the time of administration of insulin to diabetic patients. The ideal method of distributing insulin was not arrived at, but the following general rules for the management of such cases seem warranted: (a) With a maintenance diet equally distributed among the three meals of the day, mild cases of diabetes may be kept within the normal limits of glycemia by means of a single dose of insulin administered a half hour before breakfast; (b) more severe cases require, in addition to an adequate morning dose, a second but somewhat smaller one a half-hour before the evening meal; (c) when the morning fasting level of blood sugar cannot be kept below the threshold value for glycosuria by these 2 doses, a third one is indicated at about midnight; (d) the amount of

insulin to be administered at each time must be determined by blood-sugar estimations made before and after the meals. When insulin is used, as suggested in the foregoing, the highest point may be attained before the first insulin administration of the day or an hour after breakfast, while the lowest point is usually reached just before the midday meal or in the midafternoon. In all cases of diabetes, the single specimen of urine which is most likely to show sugar is one voided from one to two hours after breakfast."

Leprosy Work at Culion.—GENERAL LEONARD WOOD, Governor-General of the Philippines, has recently sent out a circular letter which embraces several reports on the colony at Culion by different observers. These reports are of interest because they give some idea of the size and of the difficulty in administering this huge leper colony. Medical men in this country may in many instances be unaware that on the island of Culion, P. I., the Government of the Philippines has segregated in a colony some 4100 lepers. Here the lepers are absolutely isolated from the well, they are given modern treatment and all their wants are amply provided for. For those who have the inclination, the will and the strength, an opportunity is given to engage in light farming or in some trade, and for the children good schools are provided. Of particular interest to the physician is that since sufficient funds for adequate treatment have been provided, more than 200 patients have been discharged as negative, 56 per cent are improved and 36 per cent are stationary. The majority of deaths are not from leprosy but from some intercurrent infection, usually tuberculosis or nephritis. One of the great obstacles that those responsible for the segregation of lepers have to contend with, is the more or less organized effort by a sentimental minority to do away with segregation. The argument is that the disease is one of the least contagious of diseases and that isolation is not necessary. It would be advisable for medical men to combat this impression whenever met. It is true that contagion is relatively difficult, but every case of leprosy is a potential focus for the dissemination of the disease and if the disease is ever to be eradicated all these foci must be segregated from contact with the healthy.

The Influence of Food Intake on the Enzymatic Concentration of Human Intestinal Contents Obtained from a Duodenal Fistula.—A young adult negro, aged twenty-three years, was admitted to the Charity Hospital, New Orleans, with a gun-shot wound of the abdomen. He was operated upon, but a few weeks later developed a duodenal fistula. As a result of this train of events, the opportunity presented itself to D. N. SILVERMAN and W. DENIS (*Arch. Int.*, 1925, 35, 357) to study the influence on the pancreatic secretion of different foods taken by mouth under conditions uninfluenced by extraneous factors such as the presence of the duodenal tube in the stomach. A summary of the findings are most suggestive. Milk, which contains fat, protein and carbohydrate, stimulated the secretion of protease and lipase. Fat, in the form of cream, brought about a distinct stimulation of the amylase and protease within twenty-six minutes and twenty minutes later a marked increase in the lipase concentration. Almost pure protein, eight egg whites and one yolk, produced the most pronounced

reaction and all three of the enzymes reached the maximum concentration of any of the experiments. In seventy-seven minutes the amylase and protease had almost doubled their concentration and the lipolytic activity rose from 0 to 1.55 cc. Arrowroot biscuits, as a test for starch stimulation of pancreatic enzymes, caused only a slight stimulation of amylase production and but little more on protease.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Lesions of the Tibial Tubercle. (Osgood, Schlatter's Disease).—POMERANZ (*Amer. Jour. Surg.*, 1925, 39, 17) says that the present conception of the disease is varied. As a result of the somewhat acrimonious debate, chiefly in the German literature, both infection and trauma have been postulated as causative factors. As is well known a periostitis may be produced by local injury or local infection. There are therefore three causes, all different, each of which may be productive of a similar roentgenographic appearance. Avulsion of the pretibial tubercle occurs most frequently in the adolescent. The disease is more common than is generally supposed. The absence of acute symptoms explains the scarcity of case reports. The architecture of the joint is such as to safely withstand moderate trauma. Most of the cases comprising this report occurred in males and in the left knee, which is at variance with reports of other writers. The lesions are most commonly traumatic, although 2 cases of the infectious type are here reported. Dense reactive sclerosis occurs in old lesions. The types of cases vary according to severity of trauma from simple strains or avulsions of the periosteum to complete avulsion of the tubercle with fragmentation of this process.

Pathogenesis of Skeletal Tuberculosis.—KOLODNY (*Jour. Bone and Joint Surg.*, 1925, 7, 53) states that the result of his investigation in relation to the most frequently involved skeletal regions in tuberculosis speak in a simple and positive way for the embolic theory of the pathogenesis of bone tuberculosis. When the blood supply is richer, other features being equal, there is a greater possibility of tuberculous involvement and hence the primary focus in these regions is more frequent. The constant strain and stress, even of a physiologic nature, has something to do as an etiologic factor in bone tuberculosis. It is evident that tuberculosis most frequently affects those parts of the skeleton which are especially adapted to the function of support and locomotion of the body, and which are under almost permanent physiological strain.

Acute Pancreatitis.—MOYNIHAN (*Ann. Surg.*, 1925, 81, 132) believes that acute pancreatitis is the most terrible of all the calamities that occur in connection with the abdominal viscera. The suddenness of its onset, the illimitable agony which accompanies it and the mortality attendant upon it, all render it the most formidable of catastrophes. The clinical picture presented by a case of acute pancreatitis is quite unmistakable. The first and chiefest symptom is pain and of all the pains that the human body can suffer, this is by far the worst. The pain is remarkable in that it comes so frequently after a good meal. It is of the fiercest intensity in the epigastrium but it is felt also in the back and often in both loins. The patient is prostrate, faint and pallid and suffers indescribable anguish. The pulse may be hardly perceptible, the limbs and face are cold and death itself seems imminent. There is all the collapse that even the greatest hemorrhage could cause and more than the agony of a visceral rupture. Tenderness is more acute above the umbilicus than below and often is far more exquisite to the left of the middle line than to the right, a point not without significance. The rarity of the condition is stressed. The anatomie and physiologic researches of Mann and Archibald are fully analyzed.

Roentgenological Aspects of Brain Tumors: Meningiomas.—SEAMAN and PUTNAM (*Am. Jour. Roentgenol.*, 1925, 12, 1) say that the pessimism in regard to the possibility of localizing cerebral tumors (exclusive of pituitary tumors) by roentgen examination is doubtless founded on the impossibility of visualizing them directly in the great majority of cases. The roentgenological findings in a group of 95 verified intracranial meningiomas have been reviewed. Approximately half of these cases showed recognizable changes characteristic of tumors. The bony changes, considered characteristic, are: Erosion and vascularity, spicule formation, diffuse thickening and enlargement of the meningeal channels. These changes are most frequently and clearly seen in meningiomas of the vault. Tumors about the sella are apt to cause a nonspecific distortion and destruction of the clinoids. Tumors of the base are often accompanied by a diffuse thickening of the floor of the skull. Those arising from the falx, from about the sella or from the sinuses of the posterior fossa, are least likely to give any indication of their presence.

A Case of Cerebral Abscess Complicating Abscess of Lung.—BARLING (*Lancet*, 1925, 1, 121) believes abscesses are nearly always in the hemisphere and often near the cortex, but have been found in the cerebellum, medulla or pons. Schorstein points out that in his collected cases, the left side of brain is affected more than twice as frequently as the right. There is pathological obscurity surrounding the association of brain abscesses with lung disease. The predominance of left-sided abscesses is in favor of the embolic origin of the infection and may be compared to a like preponderance of left-sided brain infarcts in valvular disease of the heart. The abscesses are sometimes single, sometimes multiple. Metastatic brain abscesses in general appear to be more commonly multiple, but in the group of pulmonary cases the single abscesses appear to predominate. The debilitated condition of the patient, the difficulties of localization, which are undoubtedly greater than in case of traumatic or otitic abscesses, are all against a successful

result. At the same time, when the postmortem findings in a number of these cases are studied, one cannot help feeling that some might have been cured had they been operated upon.

Acute Dilatation of Stomach and Intestinal Tube with a Consideration of "Chronic Duodenal Ileus."—ROBERTSON (*Surg., Gynec. and Obst.*, 1925, 40, 206) says that the acute cases can be divided as follows: Those in which the dilatation occurs without any apparent cause and in which, after death, no other lesion is found; those in which, after death, some definite lesion is found; those in which the dilatation follows some surgical operation and in which, after death, no other lesion is found; those in which dilatation follows an injury. The condition known as chronic duodenal ileus has been brought prominently before the profession of late. It is attributed to the constricting pressure of the superior mesenteric vessels as they cross the duodenal wall. It is indicated by a series of symptoms; obstinate dyspepsia with fulness after eating, frequent attacks of bilious vomiting, migraine, constipation, loss of weight and general abdominal discomfort. It is said to be a prominent feature of general visceroptosis. The operations proposed for it vary from a fixation of a mobile cecum to an anastomosis of the gut across the main trunk of the vessel or mesenteric root—a duodeno-duodenostomy. The author feels strongly that the "superior mesenteric artery pressure theory" will fade until it disappears entirely. Consequently he is opposed to this operation.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,
NEW YORK.

Protein Therapy and Surgical Treatment of Gastric and Duodenal Ulcers.—From the treatment of 300 cases in three years PRIBRIM (*Deutsch. med. Wchschr.*, 1925, 4, 141) concludes that protein therapy should be tried in all cases of gastric or duodenal ulcer. The theoretical basis for this form of treatment rests on the fact that inflammatory tissue has an increased susceptibility to irritation and the focal reaction which occurs after protein injection results in the healing of the ulcer and also on the belief that the irritability of the sympathetic nerve supply to the stomach is diminished with a resulting increase in the circulation of the ulcerated area. Practically, after protein therapy there is relief of pain and spasm, and a more rapid emptying of the stomach, which permits a quicker resumption of a full diet. The best results can be expected in ulcer of the lesser curvature, and in old indolent ulcers, and ulcers situated near the pylorus, although the latter show a tendency to relapse. Duodenal ulcers also show a greater tendency to relapse, and require more frequent courses of treatment. From 50 to 70

per cent of all ulcers can be satisfactorially treated by protein injection. Postoperative jejunal ulcers are not successfully treated. Recent hemorrhage is not a contraindication; on the contrary, hemorrhage may be checked. Chronic bleeding-duodenal ulcers require radical resection. Acute or subacute tuberculous processes are absolute contraindications to this form of therapy. Pribrim's conclusions are drawn from the intravenous injections of Novoprotein (Grenzach). Doses from 0.1 cc to 1 cc are given at two- or three-day intervals, and the dose should be large enough to give a focal reaction without objectionable symptoms. A course of treatment consists of not more than ten injections and after a rest of four to six weeks another course is begun. If after two or three courses of treatment there is not distinct improvement with absolute freedom from pain, ability to work and eat a regular diet, surgical treatment is indicated.

Further Report on the Combined Calcium-digitalis Treatment of Cardiac Patients.—Since the original report of GUSTAV SINGER (*Therap. Halbmonatsch*, 1921, No. 24) on the combined calcium digitalis treatment of cardiac cases almost all cases of cardiac decompensation in his clinic have been so treated, and HELLMANN and KOLLMANN (*Therap. d. Gegenw.*, 1924, 10, 444) report the results and the advantages of this form of therapy. As most of these cases require prolonged digitalis therapy cumulative poisonous effects and toxic symptoms frequently develop. When combined with intravenous calcium injections digitalis can be given over long periods without the usual signs of digitalis poisoning. In addition to the usual cases of cardiac decompensation due to myocardial changes they have also successfully treated patients with high blood pressure and cardiac decompensation, and cases of decompensation due to lesions of the aortic valve. Ampules containing a 10 per cent sterile solution of calcium chloride (Merck) were used. Of this solution $\frac{1}{2}$ cc, 2 cc to 5 cc were injected intravenously, while digitalis was administered by mouth or given intravenously if necessary. The frequency of administration and the amount of calcium given varied with the clinical condition of the patient, but from 0.1 gm. to 0.5 gm. was usually given every other day. As calcium is eliminated by way of the intestinal tract marked constipation must be prevented by enemas or administration of magnesium.

Some Observations on Blackwater Fever.—Blackwater fever is the result of malignant tertian malaria and CARMODY (*Brit. Med. Jour.*, 1925, 1, 106) reports the results of the treatment of 36 consecutive cases. He believes that a chronic anemia due to the malarial infection is fulminated by some sudden lowering of the patient's vitality; this leads to a temporary rapid hypotonic osmotic condition of the blood plasma, and bursting of the red blood corpuscles with the resultant characteristic dark urine. The successful treatment of this condition depends particularly on taking care not to move or shake the patient, and the immediate subcutaneous injection of normal saline solution. Five to ten ounces of normal saline are injected subcutaneously and repeated if necessary, but the urine usually clears quickly after the first injection. He then prescribes $\frac{1}{2}$ to 1 ounce of magnesium sulphate to be taken at the beginning of the attack and every hour 20 gr. of

bicarbonate of soda are given by mouth. Quinin is not given as a rule, but if acute symptoms of malaria are present it is best given by intramuscular injection. Even in the mildest cases the patient should be kept in bed for at least fourteen days. Of three deaths in the 36 cases reported by Carmody only one was due to blackwater fever, and as the result of moving the patient on the third day of the disease.

Iodin in Exophthalmic Goiter.—Although the exact knowledge of the etiology of goiter is still unknown the pathology of exophthalmic goiter shows an irregular and exaggerated hyperplasia of the thyroid gland, and in such cases the iodine content of the gland is extremely low. FRASER (*Brit. Med. Jour.*, 1925, 1, 1) reports the results of the administration of iodine to 24 cases of exophthalmic goiter and concludes that iodine may cause a decided, but temporary improvement in the objective and subjective symptoms, but that the dose must be small and carefully regulated. He used a 10 per cent tincture of iodine without the addition of iodide and gave at first 15 minims a day. As soon as improvement was noticed this amount was reduced to 3 to 6 minims daily, regulating the amount according to the condition of the patient. With this treatment there was a lowering of the basal metabolism, reduction of the heart rate, and increase of body weight, and improvement in the general condition of the patient. Large doses were shown to be harmful, but the smaller doses could be given almost indefinitely and when combined with surgery the results were striking. Iodine administration in exophthalmic goiter would justify the view that there is an iodine deficiency in this condition relative to the needs of the body.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Celiac Disease (Chronic Intestinal Indigestion).—SAUER (*Am. Jour. Dis. Child.*, 1925, 30, 155) outlines the care of these cases. He feels that hospital care is obligatory, if proper nursing care and coöperation cannot be obtained at home. The patient should be kept in bed until the weight exceeds by several pounds the child's maximum weight before the illness began. Extremes in room and outdoor temperatures should be avoided, and the bedding and clothing should be suitable for the season of the year. He recommends a simple high protein diet which is low in carbohydrate and fat divided into three phases. He first gives concentrated protein milk exclusively. In the second phase there are added to the protein milk certain protein foods such as curds of buttermilk or of skimmed milk, buttermilk, eggs, lean meat and boiled tongue. During the third phase there are cautiously added dextrinized starches such as flour ball, patent barley flour, imperial

gratum, arrowroot crackers, and later finely rolled zwieback or toast, and finally powdered spinach and such sugars as dextrose, dextrimaltose and corn syrup. The number of calories must be ample to ensure a continuous gain in weight. This would require of from 40 to 60 or more calories in twenty-four hours. At first the number of level packed tablespoonfuls of powdered protein milk should approximate the number of pounds the child actually weighs. Gradually this is increased to approximate the theoretical number of pounds the child should weigh for his height. In much retarded infants it may be necessary ultimately to use as many tablespoonfuls as the child should weigh for his age. The tolerance for carbohydrate and fats should never be overstepped. Fresh cow's milk, cream, butter and meat fat must be omitted for many months. If exacerbations occur should be omitted for years. Anorexia, abdominal distention, diarrheal or foamy stools necessitate the omission of carbohydrates, fats, fruits, vegetables and cod-liver oil. After an interval they may again be cautiously added. In exacerbations without apparent dietary or climatic causes, parenteral infections should be searched for, as tolerance decreases during such intercurrent diseases as pyelitis, pertussis and bronchitis.

Acidification of Milk with Vinegar.—DUNHAM (*Am. Jour. Dis. Child.*, 1925, 30, 200) describes this method of acidulating cow's milk. This is added to counteract the effect of the buffer substance of the milk on the gastric acidity. The use of acetic acid in the form of household vinegar lessened the cost of acidulation, utilized a common and harmless article of the kitchen for this purpose and made the grocery store the source of supply. A pint of vinegar milk was made from 1 ounce of vinegar, containing 5 to 6 per cent acetic acid, to 15 ounces of cow's milk. The vinegar milk was given undiluted, except to infants younger than two months who received 4 ounces of water or gruel in the total daily feeding. Corn syrup diluted with an equal amount of water was added in the amount of 1 ounce of the diluted syrup to the pint of vinegar milk. The daily amount of the diluted syrup seldom exceeded $1\frac{1}{2}$ ounces and this was reduced after cereal feedings were begun. This mixture was well tolerated as a routine food. Disturbance of the digestion was a rare occurrence, and was correctable by a temporary reduction of the sugar and fat elements of the food. The clinical results of feeding vinegar milk compare favorably with those of other types of acidulated milk. In this series some forty infants, chiefly of hospital and dispensary type were under observation on this mixture for periods of from one to six months. In no instance was it found necessary to change the type of feeding. The ages at beginning this diet ranged from four days to thirty-two months. The diagnoses included boarding babies, regulation of the diet, infantile atrophy, pylorospasm, syphilis, rickets and parenteral infections. The general appearance, contentment, nutrition, tissue turgor, musculature and rate of growth of the infants compare favorably, and in general parallel those on lactic and citric acid mixtures. The digestion was good. No abnormal amount of vomiting nor flatulency was observed. Substitution of vinegar for or by the other acids was sometimes made noticeable signs. Refusal of the mixture was not noted in any of the hospital cases. The stools

usually averaged from 2 to 3 daily and were of soft yellow consistency without free fat. In some instances where the amount of acid was less or the quantity of syrup was more than that recommended, frequency of the stools and intertrigo of the buttocks occurred. A return to the normal proportions usually effected a return to the normal digestion. Occasionally intercurrent parenteral infections were accompanied by indigestion with free fat in the stools. Replacement of the whole vinegar milk by skimmed vinegar milk and a reduction or temporary omission of the syrup was the dietary alteration of choice. In well babies changes in formulas were very infrequent. Usually one mixture would suffice for a period of from four to six weeks before another raise of from 2 to 4 ounces was necessary.

The Dick Test and Immunization Against Scarlet Fever.—NESBIT (*Jour. Am. Med. Assn.*, 1925, 84, 805) has tested 2162 cases. Of these 927 were males and 1235 were females. Among the males 40 per cent were positive, 9 per cent were slightly positive, and 50 per cent were negative. With the females 40 per cent were positive, 12 per cent slightly positive and 48 per cent negative. Seven per cent reported having had scarlet fever, and of these 28 per cent were positive, 12 per cent were slightly positive and 60 per cent were negative. The severest reactions that were observed were 3 cases of urticaria. This developed soon after the administration of the toxin. In one school following the administration of toxin to 67, no pupils lost any time. In another school, 68 first doses were given, and 1 pupil stayed home half a day on account of a sore arm. Another pupil was reported to have had a rash with a mild illness after this dose. In the same child the second dose was followed by only a mild local reaction. The third dose was followed by a fever; two days later an eruption occurred and a diagnosis of chickenpox was made which was probably the cause of the fever she had rather than the toxin. German measles was prevalent in some of the schools. This made it difficult to keep trace of every rash. In one school 57 children were given the Schick and Dick tests at the same time. Every child was present the next day for the reading of the Dick test. Notices were not sent out to parents of the time that the tests would be given, as the children behave better when parents are not present. When the test was given, notice was sent home that the test had been given and that it was necessary for the child to be back at a specified time for the reading. Nesbit found the Dick test a satisfactory method of determining persons susceptible to scarlet fever. He feels that immunization without previous tests is not justified as a routine. The 3 doses of scarlet fever toxin given seemed to immunize about 65 per cent of the pupils. The group found to be still slightly positive on retests is probably slightly immune, but to determine this final tests with controls are required. In his experience so far no case of scarlet fever has developed in any person pronounced probably immune.

Therapeutic Results with Concentrated Scarlet Fever Antitoxin: A Preliminary Report.—DICK and DICK (*Jour. Am. Med. Assn.*, 1925, 84, 803) describe their technic in preparing and standardizing scarlet

fever antitoxin. In testing the antitoxin in a control group it was given in the cases that appeared most severe when they were first seen. The cases that were less severe during the first days of the disease were used as the controls. Mild cases were not included in the group. The cases classed as moderately severe were those patients in whom the oral temperature was at least 102° , and in whom there was a moderate degree of toxemia. The cases classified as severe were characterized by high temperature with stupor, delirium or severe septic complications. In these two groups there were twice as many cases in the severe or antitoxin group as there were in the milder or control group. To be of much value in the routine treatment of scarlet fever, a serum should have some influence on the frequency of complications. In the antitoxin group there were 2 cases of otitis media. No complications developed in those that received antitoxin on the first day of the rash. There were no cases of nephritis. The results were not so good in the cases without antitoxin. In the severe cases there was 1 death in the antitoxin series. This was due to a neglected mastoid infection. There was 1 case of marked cervical adenitis in a patient who received the antitoxin on the fifth day of the disease, when the glands were already enlarged. In studying these cases they were impressed by frequency of sinus infections in the more severe types of scarlet fever. Sinusitis was diagnosed clinically in 10 per cent of the moderately severe cases and in 58 per cent of the severe cases with marked toxemia or septic complications. In this series there was evidence that the sinus infection preceded the attack of scarlet fever or was coincident with it. It is possible that absorption of large amounts of toxin from the infected sinuses accounts for the severity of such cases. For the present two doses of antitoxin are given to patients with marked toxemia associated with sinusitis or in severe cases with septic complications. The best results were obtained when the total amount of antitoxin administered was given in one dose early in the disease. The antitoxin was given intramuscularly. Patients with a previous history of administration of horse serum were given preliminary small desensitizing doses before the therapeutic dose was injected. In early cases the rash is the most convenient indicator of the action of the antitoxin. If enough antitoxin has been given, the rash will fade definitely within twenty-four hours. There will be a marked improvement in the general condition of the patient, especially noticeable in the most toxic case. This improvement is accompanied by a fall in the temperature. One effect of the antitoxin is the unmasking of such complications as are already present. The removal of the toxic element of the disease makes the recognition of and the proper treatment of early complications more certain. The serum reactions in this series were comparable in every way with the reactions following diphtheria antitoxin. Any reaction to the serum is uncommon in persons who give no history of previous administration of horse serum.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

End-results after Operation for Uterine Prolapse.—GRAD (*Am. Jour. Obst. and Gynec.*, 1924, 8, 163) has operated upon 53 cases of prolapse of the uterus using eight different operations; an average of $3\frac{5}{8}$ operations were required for each case of prolapse. Of the 53 cases, 66 per cent had the cervix amputated; 79 per cent had an anterior colporrhaphy; 94 per cent had perineorrhaphy; 43 per cent had interposition; 41 per cent had the uterosacral ligaments shortened and 13 percent had vaginal hysterectomy. From these experiences the writer concludes that childbirth is the cause of prolapse of the uterus. In 21 per cent of cases the condition develops after the first childbirth, and in 72 per cent the prolapse is of the third degree. Among these patients 39 per cent had prolapse after two or more children and of these 71 per cent had the third degree of prolapse. It could not be shown that instrumental delivery had anything to do with the production of uterine prolapse from the 41 per cent of instrumental deliveries, contrasted with the 59 per cent without instruments. As the age of the patient advances, the number of cases of extensive prolapse increases. Many of these cases were complicated by other conditions, and there is a mortality rate which accompanies operations upon these patients. Where the prolapse is pronounced in position, operation is useful. As to the results, the writer had 75 per cent of successes in his cases.

Yellow Spinal Fluid and Jaundice in the Newborn having Intracranial Hemorrhage.—SHARPE (*Am. Jour. Obst. and Gynec.*, 1924, 8, 186) has studied this question for some time and finds, after repeated autopsies, that the intracranial anatomy of the bloodvessels in the newborn child differs from that of the adult, and that the newborn is much more susceptible to injury. When intracranial bleeding occurs, it is from one of three causes: From trauma, congestion, asphyxia or blood-disease of the newborn. Contrary to what is often alleged, syphilis, maternal toxemia, early low forceps applications and hemorrhagic disorders of the newborn are comparatively unimportant in causing cerebral hemorrhage. The signs vary, depending upon the amount and the location of the intracranial hemorrhage and edema. The mildest cases are usually overlooked and the routine lumbar puncture yielding bloody spinal fluid gives the first information concerning the condition. In one hundred consecutive deliveries 10 per cent had spinal fluid containing evidences of intracranial injury. In 4 this fluid was bloody, in 6 yellow, and in only 4 of these could red corpuscles be demonstrated. The condition of the anterior fontanelle is not a reliable index of a mild increase in the intracranial pressure. He distinguishes three

types of yellow spinal fluid: xanthochromia, erythrochromia and nonne syndrome. In this series, 6 cases contained yellow spinal fluid which probably results from the transudation of blood plasma when red corpuseles are absent; caused by minute hemorrhages when red blood corpuseles are present. In this series were 4 cases of icterus neonatorum, and only 1 had yellow spinal fluid in the writer's experience. Early lumbar puncture should be employed in the absence of shock, not only for diagnosis, but for its therapeutic value in cases of early cerebral hemorrhage and edema. Repeated spinal drainage every twelve to twenty-four hours is indicated, depending on the size of intracranial bleeding or the amount of cerebral edema as registered by the spinal mercurial manometer. The author employs a modified subtemporal decompression with cranial drainage only when drainage by lumbar puncture fails. In all suspected cases of hemorrhage in the newborn, manometric readings of intradural pressure should be taken with the spinal mercurial manometer.

A Contribution to the Genesis of Hydatid Mole.—KELLER (*Gynec. et Obst.*, 1924, 9, 68) in 7 cases of hydatid mole found the characteristic degeneration in the villi, having its origin in anomalies in the circulation of the part. In the villi in moles it is remarkable that vessels are almost completely absent; what remains is the lacunæ, which are the original blood channels. The origin of these variations in circulation is not readily explained and is largely a matter of further histological study. In the same journal and from the Strassburg Clinic, RIEHL contributes a paper on "Marginal Placentæ." This contains illustrations with the report of microscopic study of the cases and statistics cited from other clinics. The writer's personal statistics are based upon 116 observations; 62 primiparæ, 53.44 per cent; 35 secundiparæ, 30.17 per cent; and 5 cases pregnant for the third time. The writer concludes that the important factor in these cases is the fibrous ring made up of fibrin of different development, some of it dense, some of it canalized and some marked by reticulation; in others the villi are more or less necrosed while still other specimens show the decidua cells in a necrotic condition more or less pronounced, with hemorrhage. In the first group of these marginal placenta this fibrous ring is produced by the stagnation of blood in the intervillous space at the periphery of the placenta. In the second group this fibrous ring develops at the end of the sixth or seventh month by unequal development of the two placental surfaces. There follows an extra-chorial margin between the two placental surfaces. The third group of these placenta, which is rare, is found where the placenta is inserted into the uterine cornu. This tubal insertion is accompanied by separation of the chorionic base of the superficial villi at the border of the placental lobe which covers the orifice of the tube. This is accompanied by hemorrhage and by the deposit of fibrin and by necrosis of the superficial villi. The result of these alterations is the formation of the fibrous ring, which is practically extra-chorial. A small number of these placenta are formed by the persistence of a portion of the decidua reflected at the margin of the placenta. From the clinical point of view, marginal placenta occur most frequently with primiparæ and secundi-

paræ. This marginal placenta can be the cause of hemorrhage during pregnancy. These hemorrhages, accompanied by pain in the lower abdomen, can cause separation of the placenta which, in the greater number of cases, is partial. In some very rare cases it is total and is followed by premature labor. There is a distinct causal relation between marginal placenta and premature separation of a placenta normally inserted. In other cases placental separation is the consequence and not the cause of hemorrhage. This is seen in marginal placenta inserted at the tubal orifice. These cases are frequently not recognized until the moment of delivery. In addition to rupture of the membranes in 116 of these cases, the author had seventeen in which atony of the uterus accompanied this condition. This complication was five times more frequent in these than in normal cases. The writer's studies do not indicate that this condition influences the development of the fetus.

Sudden Death following Labor.—An interesting contribution to sudden death with shock following labor in a toxic woman is made by SCHICKELE from his clinic in Strassburg (*Gynec. et Obst.*, 1924, 9, 123). The patient was aged thirty-five, and in her second pregnancy; spontaneous labor was followed by hemorrhage and manual removal of the placenta, with good uterine contraction. Moderate anesthesia with ether had been employed and after delivery the patient complained of dyspnea, became gradually cyanosed, the pulse rapidly failed and an hour after delivery death occurred. Autopsy revealed an interesting condition. The substance of the liver was extensively disintegrated and necrotic. This degeneration was of different degrees at the periphery of the hepatic globules. The kidney lesions were unimportant and the manifestations of toxemia in the kidneys were in the first stage only. The patient did not give the slightest indication of eclamptic convulsions or threatened convulsions. The second case was that of a young woman whose labor lasted fifteen hours, terminated by a low forceps application followed by a temperature of 100.5° F. The extraction of the child was easily accomplished, the child was living and vigorous and the delivery was apparently without complications. An hour after the birth of the child the patient became suddenly pale, the pulse failed, there was no hemorrhage and four hours after delivery, sudden death. Autopsy revealed extensive lesions of the liver, no embolism, no lesions in the heart or other organs which would have produced such a result. Eight weeks before labor the patient had a fall which gave her a severe shock, but from which she recovered, and there was no evidence that this fall had anything to do with the fatal issue. At autopsy the liver showed extensive disintegration, dilatation of the capillaries, multiple hemorrhage and various stages of cellular degeneration. The kidney lesions in this case were very slight and there were some small hemorrhages in the cortical portion of the suprarenal capsules. This case showed at autopsy some of the lesions in the liver typical of eclampsia, but there were no symptoms of convulsions. The third case was a woman in her fourth pregnancy, with rachitic pelvis, Cesarean section, spinal anesthesia. The delivery of the child was complete in six minutes after the beginning of the operation under perfect anesthesia, when the pulse suddenly failed, the patient became

livid, respiration ceased and death ensued in a few moments. It was thought that the spinal anesthesia might have been the cause of the sudden death. Autopsy showed hyperemia of the abdominal organs, no lesions of the lungs, heart or kidneys, but in the liver the signs of yellow atrophy often seen in eclamptic cases. Microscopical examination showed at the periphery of the acini multiple foci of necrosis with fatty degeneration. The drug used in the spinal anesthesia was synecin.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, -

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Irradiation Treatment of Urethral Caruncle.—A urethral caruncle, a small thing in itself, at times gives rise to no symptoms and may be discovered only in the course of a routine examination, but in many cases it cause burning, itching or even intense pain on urination. The old treatment of excision of these small tumors was often disappointing and frequently followed by recurrence. POMEROY and MILWARD (*Am. Jour. Roentgenol.*, 1924, 12, 524) believe that they have attained their best results in the treatment of this condition by the use of radium. In their work nitrous oxide anesthesia is used because of the exquisite local tenderness and to permit a thorough pelvic examination. A small portion of the growth is excised for microscopic examination and the electrocautery is applied to the bleeding spot left at the site of the excision. They then apply screened radium to the urethral canal using 50 mg. of radium element screened with 0.5 mm. silver, 1 mm. brass and 1 mm. rubber, and the insertion of enough 5 mg. steel needles to occupy the growth and usually to surround the urethral canal. A sponge is placed over the meatus and the labia united over this by a removable suture passed through the outer end of the rubber covering the tube in the urethra. The radium is allowed to remain in position, three to six hours, one treatment usually being sufficient. There is considerable local reaction after the treatment but this soon subsides and there have been no recurrences where this dosage has been used. They have not embedded unscreened emanation seeds in these cases but they believe that such seeds are suitable where the caruncle is sufficiently large to protect, by its size, the neighboring portions of the vulva from the buried emanation.

Milk Injections in Pelvic Infections.—For several years GELLHORN (*Am. Jour. Obst. and Gynec.*, 1924, 8, 535) has been using parenteral protein therapy in the form of milk injections in the treatment of various

kinds of pelvic inflammations. He states that not all parts of the genital tract respond equally well to these injections. The tubes, the uterus and probably the bladder are favorably influenced while the ovaries seem to remain refractory. Exudates are brought to absorption or else a circumscribed suppuration is hastened so that they can be attacked surgically, but adhesions are not affected. Gonorrheal infection of the cervix, as a rule, remains likewise untouched by the treatment and the same may be said of gonorrheal foci in the urethra and rectum, which must be treated separately to prevent reinfection. The site of injection of the milk is preferably the gluteal musculature and if the needle is thin and sharp and the injection is made slowly, the procedure is not painful though the bulk of the fluid injected may cause a momentary discomfort. The initial dose is 5 cc, occasionally even less if the patient is very weak or the fever very high. The standard dose is 10 cc which, depending on individual circumstances, is reached with the second or third injection and then maintained through the course of treatment. The interval between injections is, as a rule, from three to five days according to the intensity of the reaction; in indolent patients it may occasionally be reduced to two days. In mild cases, 1 or 2 injections will often suffice; in others, more are required. The general reaction occurs from six to eight hours after treatment. The fever following the chill is usually of moderate degree though occasionally it may rise to 104° . The intensity of the initial reaction, which decreases after succeeding injections, is generally considered a favorable prognostic sign unless it be excessive, although satisfactory results have been obtained where there was hardly any general reaction. In any event, the general condition is affected but a very short time, twenty-four hours at most, after which the euphoria, which is mentioned by all writers is quite marked. The patients look and feel decidedly better and their appetites improve. Systematic white blood counts have revealed a hyperleukocytosis on an average of 20,000 to 25,000 on the day following the injection which receded to more normal figures within the next two days. An anaphylactic shock has never occurred in Gellhorn's cases and he does not anticipate any. While this alarming complication has been observed after intravenous injections of casein, only 3 such cases have been reported among the many thousands of intramuscular injections of milk. It may be that in these cases part of the injection had accidentally reached a vein, therefore Gellhorn makes it a point, before each injection, whether the needle has punctured a vessel. In spite of the ample scope of this form of treatment, its limitations must not be overlooked. There are several absolute contraindications, such as cardiac decompensation, diabetes and alcoholism. Whether pregnancy belongs to this group is still an open question.

Total versus Subtotal Hysterectomy.—The perennial question among gynecologists is the advisability of performing a subtotal or a total hysterectomy in the treatment of uterine fibroids, providing, of course, that the uterus must be sacrificed. Many arguments have been presented on both sides of the question and well-qualified surgeons have defended each operation, much to the exclusion of the other. In a report from Vienna, HALBAN (*Zentralbl. f. Gyn.*, 1924, 48, 2674), a leading

Continental gynecologist, has analyzed the results in his clinic in a series of 342 cases. In this series there were 132 supravaginal amputations with a mortality of 4.5 per cent, 38 panhysterectomies with a mortality of 13.1 per cent, and 172 vaginal hysterectomies with a mortality of 5.2 per cent. Concerning the 13.1 per cent mortality in the series of total abdominal extirpations, presenting 5 patients, Halban states that these deaths were due to peritonitis in 2 cases, while in 2 others death was due to the severe anemia which had so affected the heart that the shock of operation could not be tolerated and he believes that these deaths should be charged against the heart rather than the operation. The fifth death was in a case in which a large intraligamentary myoma had been removed after which there was such a severe hemorrhage between the layers of the broad ligament that the internal iliac artery had to be ligated. Following this a thrombus broke loose and caused embolism of the femoral artery which was followed by gangrene of the leg. The leg was amputated but the patient died of sepsis. In the series of supravaginal amputations there were 6 deaths, 4 due to peritonitis and 2 due to myocardial degeneration. Of the 9 deaths in the series of vaginal hysterectomies, 2 were due to sepsis, 2 due to pneumonia, 1 due to severe anemia and 1 due to paralytic ileus; the other 3 deaths are not recorded. The above figures are taken from Halban's Clinic where the work was done by several operators and he begs to present the statistics of the cases which he personally operated upon over a long period of time (1911-1924). Including both myomata and myopathic hemorrhage cases, he has done 134 supravaginal amputations with 2 deaths (1.5 per cent mortality), 35 panhysterectomies with 2 deaths (5.7 per cent mortality), and 254 vaginal hysterectomies with no mortality. From these statistics it is readily seen that vaginal hysterectomy is the method of choice in Halban's hands.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
DEWAYNE G. RICHEY, B.S., M.D.,
MERCY HOSPITAL, PITTSBURGH, PA.

The Incidence and Pathogenesis of Tonsillar Concretions.—After an extensive historical review of his subject, WELLER (*Ann. Otol., Rhinol. and Laryngol.*, 1924, 33, 79) reported the results of a careful research of the sections from a series of 1000 consecutive pairs of tonsils in order to have figures which represented minimum values. While no statistical record had been kept of calculi of large size, he believed that a conservative estimate would be 2 per cent. Much more common were the calculi discovered by microscopical examination alone, 80 cases showing calcareous deposits in the crypts of one or both tonsils—an incidence of 8 per cent. The average age of the cases in the series of 1000 was 18.7 years, while the average age of the 80 posi-

tive cases was 16.8 years. The author emphasized that the incidence as found in the 1000 cases may be taken as the minimum incidence figure for the 16,000 pairs of tonsils which have been examined in their laboratory. As clinical tonsillolithiasis usually occurs in late adult life, and the average age in the positive cases of this series was 16.8 years, it would seem to indicate a relatively slow rate of growth for larger calculi. Microscopical study of the genesis of tonsillar calcareous concretions showed that such deposits may occur in any portion of the tonsil. With rare exceptions it was only in the crypts that concretions reached such a size that they became clinical tonsilloliths. In the faucial tonsils the commonest modes of origin within the crypts were in the dead interior of colonies of mouth organisms and in masses of keratohyalin—59 per cent developing in the so-called "actinomyces-like" colonies of mixed mouth microorganisms and 41 per cent in the accumulated keratohyalin masses in the crypts. These are the chief sources of clinical tonsilloliths. Vegetable material, food debris, inflammatory exudate, desquamated epithelium and old blood from hemorrhage may also serve as the organic nucleus for calculus formation in the crypts. In the pharyngeal tonsils calculus formation occurred especially in mucopurulent exudate and in keratohyalin. In the lymphoid tissue of the tonsil calcification of old blood pus or caseous necrosis was found to occur, as in lymphoid tissue elsewhere. Tonsil calculi conformed to the general laws of calculus formation in that they developed only upon an organic nucleus in a state of necrosis or necrobiosis and that they could show, although but faintly, concentric lamination and radial striation. The very common association of cholesterol crystals with the beginnings of calculus formation in the tonsil indicated that the presence of lipoids and the formation of soaps may be an important part in the chemical mode of their development. As tonsillar calculi become larger, the author concludes "Their presence favors the origin and continuation of an active inflammatory process in the wall of the crypt in which they are situated."

The Significance of the Blood Picture in the Symptomatology and Therapy of Purulent Mastoiditis.—Having found that many of the well-known symptoms—such as pain on pressure, postauricular swelling, erythema and fever—of purulent mastoiditis are unreliable and uncertain, ROSENO (*Arch. Jour. Ohren-, Nasen-, u. Kehltröpfhkk.*, 1924, 112, 30) found that the blood picture furnished a delicate diagnostic criterion of this formidable condition. In 22 cases of suppurative mastoiditis, confirmed by operation, it was found that the leukocyte count ranged from 12,000 to 16,000, while the number of polymorphonuclear leukocytes varied from 80 to 88 per cent. When complications existed the white blood cells increased to 20,000 or 22,000 and the polymorphonuclears to 90 per cent. The authors believed that this hematological evidence yielded not only valuable early objective information on the presence of purulent mastoiditis but also was an index as to the necessity of operative interference.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

ASSISTANT PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Skin Infection of Rabbits with Hemolytic Streptococci Isolated from a Patient with Erysipelas.—A serum capable of warding off the injurious action of the streptococcus on the skin is described by RIVERS (*Jour. Exp. Med.*, 1925, 41, 179). He isolated a streptococcus, whose virulence for rabbits intravenously or intraperitoneally was not marked. from a human case of erysipelas. The organism was morphologically and culturally typical of the *Streptococcus hemolyticus* and its virulence was maintained by occasional intracutaneous passages through rabbits. The bacteria from a twenty-four hour culture on blood agar were suspended in 8 cc Loeke's solution and various dilutions of this were used in the inoculations, these being made into the shaved sides of the chests and abdomens of rabbits. Marked reactions were observed varying with the concentration of the inoculum. The reactions are fully described. Immune serum was prepared by 7 successive intrautaneous inoculations of 7 rabbits, during the course of which the skin reactions became progressively less marked. The sera were collected and pooled and at the same time the sera of 7 normal rabbits were collected. To 1 cc of immune serum and to 1 cc of the normal serum were added 1 cc of a streptococcus suspension and these mixtures were injected subcutaneously each on one side of the same rabbit. In many repetitions the protective power of the immune serum was continually characteristic, the normal serum having no protective effect. The intrautaneous method of demonstrating the immune properties of antistreptococcus serum may be of value, the author suggests, in determining the potency of sera for therapeutic uses, and for testing the specificity of different strains of streptococcus. The paper is well illustrated with photographs.

The Oxydase Reaction in Acute Myeloid Leukemia.—Staining methods for the determination of the nature of white cells in the blood have been developed almost without number. This in itself indicates that there are many features in respect to the granulation of white blood cells which are not well understood, and which can only be determined by the application of suitable dyes. PINEY (*Jour. Path. and Bact.*, 1925, 28, 97) points out that there is a great divergence in the estimation of white cells depending upon the character of the stain used. It is found, for example, that specimens stained with Ehrlich's triacid stain demonstrate a greater number of neutrophile cells than when the Jenner's solution is used. It is found moreover that the oxydase reaction in the blood cells bears a direct relation to the presence of granules in the cytoplasm. Kardos had previously shown that the use of methyl green and orange G when introduced into Giemsa's solution, gave much

better results with neutrophile granules. The author has made some modifications of this stain and found it highly successful in demonstrating the myeloid leukocytes. When comparing the results of his staining in cases of acute leukemia with those of the Jenner solution it was found that the new staining method was more accurate in bringing to light slight granulation in myeloblasts which were entirely wanting in other staining methods. He found moreover that these results were in close harmony with those obtained by the oxydase reaction. The contention of the report is that the completely nongranular myeloblasts do not give a positive oxydase reaction and that the development of even a few granules in them is associated with the appearance of the reaction. It would appear that all gradations from the nongranular myeloblast may be traced to the heavily granuled myelocyte.

The Significance of Anaphylaxis in Penumococcus Immunity.—Working with a pneumococcus Type I isolated from the blood of a patient suffering from lobar pneumonia, MCKENZIE (*Jour. Exper. Med.*, 1925, 41, 53) has attempted to determine the immunological significance of anaphylaxis. His general plan was to subject guinea-pigs to immunizing injections of pneumococcus, titering the immunity at frequent intervals and testing for the appearance and duration of allergy and anaphylaxis. His immunizing injections began with heat-killed eighteen-hour cultures and changed to fresh unkilld eighteen-hour cultures, bringing the animals during the course of four or five weeks to a state of immunity in which they survived 10,000,000 lethal doses of living culture. Every five to seven days 12 to 15 animals were taken from the batch of 150 to determine the degree of immunity attained and to demonstrate the presence of specific hypersensitiveness whenever it existed. The virulence of the pneumococcus was maintained at a fixed level by weekly animal passages. In testing for skin allergy and anaphylaxis the antigens used were: (1) Eighteen-hour broth cultures killed by heating to 60° C. for one hour; (2) filtrate from fresh eighteen-hour broth cultures; (3) an NaOH extract of a centrifuged, dried and powdered eighteen-hour culture, standardized by nitrogen content. Injections were made subcutaneously and intravenously, while the uterine strip method of Schultz-Dale was also used. Findings were unsatisfactory in the last named. The protective power of the serum was quantitatively determined at each observation. It was observed that decrease in the protective power of the serum occurs just prior to the period when anaphylaxis becomes demonstrable. The significance of this was not clear. Neither precipitins nor agglutinins were demonstrable at any time during the experiment. No cutaneous allergy to the derivatives of the pneumococcus used was demonstrable at any time. There was no change in trend of the immunity curve when anaphylaxis to the pneumococcus protein appeared. A high degree of immunity and a serum with strong protective power were obtained by the author in this experiment bearing, apparently, no relation to anaphylaxis. In a subsequent paper, *The Production and Significance of Cutaneous Allergy to Pneumococcus Protein*, MCKENZIE and Woo (*Jour. Exper. Med.*, 1925, 41, 65) were unable to demonstrate any relation between cutaneous allergy—produced by intracutaneous injection of an alkaline

extract of pneumococcus products—and susceptibility to pneumococcus infection by intraperitoneal inoculation. Additional evidence in support of the idea that an allergy of the tuberculin type may be produced in the absence of an infection is brought out in the paper, although at the same time earlier studies have shown that allergy to derivatives of microorganisms is not an uncommon accompaniment of infection. The same strain of pneumococcus was employed as was used in the previous experiment. Skin allergy was easily and satisfactorily produced. Anaphylaxis was not demonstrable in these animals. Susceptibility to homologous infection in the allergic animals differed little or not at all from normal controls. The authors conclude that the relationship of allergy to immunity may vary with all types of infection and that no generalization is justifiable.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. MCCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

The Relation of Dose of Bacteria to Group Infection.—BLOOMFIELD and FELTY (*Jour. Exp. Med.*, 1924, 39, 367), suggested in a previous paper on the basis of clinical observations and test-tube experiments, that the dose of bacteria and the degree of their vegetative activity were at least two factors which were significant in determining whether or not infection will develop in a susceptible host. Clinical observations on the effect of crowding suggest that in the presence of carriers of certain varieties of pathogenic bacteria a very high degree of intimate contact is necessary before spread of infection takes place at all; that as the degree of contact is reduced, there is not a gradual falling off in the number of secondary infections, but at a certain point they diminish with great abruptness to a figure approximating zero. In other words, it seems probable that people who are relatively resistant to a certain organism must receive a dose greater than some critical value before any infection will result, and that smaller doses, even if pathogenic bacteria are actually received, for example, into the upper air passages, will be quite inadequate, other things being equal, to colonize, to invade, or to produce disease. Such an idea explains the usual harmlessness of the diphtheria bacillus, streptococcus, or meningococcus carrier. His associates acquire the organisms, to be sure, but under ordinary conditions of contact only a subcritical dose in the sense indicated above. Recent studies by the same authors (*Jour. Exp.*

Med., 1924, 40, 679) have been made of the peritoneal reaction in mice after injection of different bacteria in graded dose. Organisms were employed to which the animals were fairly resistant. Under these conditions it was found that as the dosage was decreased a more or less critical point was reached below which infection failed to be initiated. The possible clinical bearings of this observation are discussed.

Observations on the Diphtheria Carrier as an Agent in the Spread of Diphtheria.—MEADER (*Jour. Am. Med. Assn.*, 1924, 83, 1132) states that it would appear that diphtheria patients are more likely to be agents in the spread of diphtheria than are carriers, but it cannot be denied that carriers who harbor organisms capable of producing the disease may be very potent agents in the spread of infection. He believes, however, that carriers of diphtheroids who have not been associated with clinical cases of diphtheria may be disregarded from a public-health point of view.

A Comparison of Physical Defects in University Students from Rural and Urban Districts.—SHEPARD and DIEHL (*Jour. Am. Med. Assn.*, 1924, 83, 1117) examined students entering the University of Minnesota for the purpose of detecting departures from normal. The results were as follows: Students raised in villages of from 50 to 1000 population have more physical defects than students raised in other communities. Multiple defects are also common in this group. Students raised on farms show more physical defects than those raised in towns or large cities, about the same number as those from small cities and less than those raised in villages. Students raised in towns of from 1,000 to 5,000 population show less physical defects than any others except those from large cities. Students raised in small cities of from 5,000 to 50,000 population are exceeded in total physical defects only by students from villages. Students raised in cities of more than 50,000 population show the lowest number of physical defects.

Tularemia Infection in Ticks of the Species *Dermacentor Andersoni* Stiles in the Bitter Root Valley, Mont.—PARKER, SPENCER and FRANCIS (*Pub. Health Rep.*, 1924, 39, 1057) suggest that tularemia may be communicated to man through ticks. The infection has been found in immature and in adult ticks. The infection survives in the insects for a period of several months. It was found that a number of small mammals in the tick region are susceptible to tularemia and doubtless help to perpetuate it.

The Thermic and Leukocytic Response of the Rabbit to Inoculation with the Virus of Measles and their Value as Criteria of Infection.—Among the laboratory animals, monkeys, guinea pigs and rabbits have been found to be susceptible to the virus of measles. That rabbits may be successfully infected has been demonstrated by the combined investigations of Harde (1921), Nevin and Bittmann (1921 and 1923) Gründ (1922) and Duval and d'Aunoy (1922). SCOTT and SIMON (*Am. Jour. Hyg.*, 1924, 4, 559) conclude from their experiments that a sustained rise in temperature with its acme occurring at a certain time, coupled with an amphophilic leucopenia, constitute the most character-

istic symptoms of a measles infection in the rabbit, and that with proper controls the thermic and leucocytic responses may well serve as criteria of infection with this virus.

A Note on the Relationship of Tonsillectomy to the Occurrence of Scarlet Fever and Diphtheria.—DOULL (*Pub. Health Rep.*, 1924, 39, 1833) made surveys of the white school population of wards, 5, 6, 7, 8, 9 and 10 of the city of Baltimore, and found that the percentage of children having had the tonsils removed varies from approximately 7 per cent at ages five and six years to 19 per cent at ages thirteen and fourteen years. A study of a consecutive series of 224 cases of diphtheria of school age and living in the same area of the city showed that only 2 (0.9 per cent) of the children had had tonsillectomy performed. This is a very much smaller number than would be expected in a sample of this size and age distribution selected at random from the school population. In a sample of 193 cases of scarlet fever in children of school age, 19 (9.8 per cent) were found to have had the tonsils removed prior to attack. This number does not differ significantly from that expected in a random sample of the school population similarly constituted as to age. The author states that he believes the results of his studies justify the conclusion that children whose tonsils have been removed are distinctly less liable to diphtheria than those who have not had this operation performed; whereas in scarlet fever no significant difference is shown. General conclusions as to the relationship which tonsillectomy bears to either of these infections, diphtheria or scarlet fever, require more observations in other localities.

How Salt Preserves.—ROCKWELL and EBERTZ (*Jour. Infect. Dis.*, 1924, 35, 573) state that the preserving of proteins with salt involves more than its dehydration effect, there being at least four factors, namely: Dehydration, direct effect of chlorine ion, removal of oxygen, sensitization against carbon dioxide and interference with rapid action of proteolytic enzymes.

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ORIGINAL ARTICLES.

EFFECT OF PREMATURE DOGMATIZATION IN MEDICAL
SCIENCE.

ILLUSTRATED IN THE FIELD OF ANAPHYLAXIS AND IMMUNITY.

BY W. H. MANWARING, M.D.

PROFESSOR OF BACTERIOLOGY AND EXPERIMENTAL PATHOLOGY, STANFORD UNIVERSITY
SCHOOL OF MEDICINE, STANFORD UNIVERSITY, CALIFORNIA.

INTUITIVE dogmatization from inadequate data not infrequently plays a prominent role in medical science and is a major handicap in research. In no field are its effects more evident than in the field of anaphylaxis and immunity.

The success of Jennerian vaccination supplemented by statistics in other diseases led to the early intuitive generalization that artificial inoculation and natural infection invariably leave behind them an increased resistance or acquired immunity to reinfection, that physicians have but to find suitable vaccines to control all infectious processes. Although this was never more than a subconscious dogma in scientific medicine, it nevertheless dominated medical thought during the nineteenth century; was the basis of interpretation for immunological phenomena, and made possible lucrative exploitation of prophylactic and therapeutic vaccines in spite of inadequate evidence in their support. The dogma so biased clinicians that failure of a vaccine was not interpreted as evidence against the dogma, but merely as an indication that the proper vaccine had not yet been found.

The dogma also blinded non-clinical workers. Flagrant contradictions to the basal assumption were repeatedly overlooked or

ignored by laboratory men, or discarded by them as of no significance, presumably due to idiosyncrasies or to experimental errors. It would be of interest to collect from the literature of the nineteenth century the numerous examples of the blinding effect of this dogma on observational science. The most striking example thus far brought to light is that of Magendie, who, in 1839, regarded as of little or no significance acquired protein hypersensitiveness in his laboratory animals, protocols now seen to be practically identical with those for which Riehet, seventy-four years later, was awarded the Nobel Prize. During the last two decades of the nineteenth century scores of similar protocols were ignored or discarded by the foremost research workers of both hemispheres, humble tribute to the narcotizing effect of intuitive dogma.

With Behring's observation in 1890 that sera of animals immunized against diphtheria toxin have antitoxic properties sufficient to control diphtheria in the other animals, there was the further intuitive generalization that the essential defense against all infections is located in the blood stream, that foreign serum is capable of harmonious coöperation with the normal defenses of the human body, and that physicians have but to find suitable sera to control all infectious diseases. This intuitive dogma made possible lucrative exploitation of alleged prophylactic and curative sera in spite of inadequate evidence in their support, and so blinded clinicians that failure of a serum was not interpreted as evidence against the dogma, but merely as an indication that the proper serum had not yet been found.

The dogma also dominated theoretical research. For three decades immunology developed almost solely along serological lines, a juggling of shifting hypotheses to fit the major premise that all immunological phenomena are due to serum changes, ignoring the possibility that essential immunity factors might be located in the fixed tissues. That fixed tissues often play a dominant role in immunity is now generally realized. Transfusion of practically the total blood volume of an immune donor will not always confer immunity upon the recipient.¹

With the observations of Riehet and of Arthus in 1902, that animals injected with foreign protein often become hypersensitive, reinjection causing violent local or systemic reactions, there was the further intuitive dogmatization that all infections leave behind them a subnormal resistance to reinfection superimposed upon the assumed immunity factors, that vaccines and sera are of use only in those diseases in which the immunity factors can be made to dominate. This basal conception of two antagonistic mechanisms, a superposition of anaphylactic and immunity factors, is the preva-

¹ Manwaring, W. H., and Bronfenbrenner, J.: Intraperitoneal Lysis of Tubercle Bacilli, *Jour. Exper. Med.*, 1913, 18, 601.

lent current conception of the relationship between anaphylaxis and immunity.

Recent experiments lead one to question the validity of this conception, to wonder if it in turn is not an intuitive dogma, seriously handicapping theoretical and practical medicine. Opie,² for example, finds that local anaphylaxis serves the useful purpose of preventing the absorption of specific foreign protein from the site of injection, thus protecting more important internal parts. A paradox of an apparently subnormal local resistance playing a purposeful role in systemic immunity.

It would not take an oriental imagination to picture all known anaphylactic phenomena in this light. The vascular reactions on which the Arthus phenomenon depends could thus be looked upon as purposeful physiological reactions designed to prevent the absorption of unwelcome proteins, a source of serious danger to the individual only under the artificial conditions of current anaphylactic research, intravenous injection of overwhelming doses of specific foreign protein. The characteristic anaphylactic bronchial reactions could be pictured as purposeful physiological defenses preventing the entrance of unwelcome agents into the pulmonary alveoli, a source of danger only on massive intravenous injections, throwing all parts of the bronchial tree into simultaneous constriction. The intestinal and esophageal reactions, as purposeful mechanisms for the rapid removal of unwelcome gastro-intestinal contents. The hepatic reactions, as purposeful adaptations for the rapid destruction or elimination of unwelcome products from the blood stream.

That this conception of the fundamental relation between anaphylaxis and immunity is more than a mere poetic conception, is indicated by the fact that, so far as tested, the immunity reactions of isolated fixed-tissues are identical with the so-called anaphylactic reactions. Typical anaphylactic responses are given by immune tissues on perfusion with normal blood plus specific foreign protein.³ This conception of the essential identity of anaphylaxis and immunity would render obsolete the entire current nomenclature of anaphylaxis.

Study of the anaphylactic responses of fixed tissues, therefore, is of vital interest to theoretical and practical medicine, and may furnish facts on which the immuno-therapy of the future may largely depend.

² The Relation of Local Sensitization to Immunity, *Jour. Immunol.*, 1924, 9, 259.

³ Manwaring, W. H. and Kusama, Y.: Analysis of Anaphylactic and Immune Reactions by Means of the Isolated Guinea-pig Lungs, *Jour. Immunol.*, 1917, 2, 157.

IS OUR KNOWLEDGE OF PNEUMONIA SUFFICIENT TO EX-
PLAIN ITS ENDEMICITY AND OCCASIONAL
EPIDEMICITY?*

By A. C. ABBOTT,

DIRECTOR SCHOOL OF HYGIENE, PUBLIC HEALTH, UNIVERSITY OF PENNSYLVANIA.

As I view the current problem of pneumonia our knowledge of that disease is, in a number of important particulars, so defective that definite conclusions are difficult, if not impossible. It is with the intention of indicating what I regard as some of these deficiencies and of offering certain suggestions for further investigation, that I accept your kind invitation to take part in this discussion.

If the views that I express are not altogether in harmony with those commonly held, it is because I am convinced that the studies thus far made of pneumonia have not been sufficiently comprehensive. While they have shed much light upon the character of the pulmonary lesions and have offered many helpful suggestions as to the causation of those local conditions, I cannot avoid the opinion that they have done but little in clarifying the larger problem of the origin of pneumonia as a constitutional and probably transmissible disease; and insofar as they enable a full and complete discussion of either the epidemiology or the endemicity of pneumonia, I am sure you will agree with me that they are insufficient and often may be misleading.

Such reliable data as are available upon the strictly epidemic features of this disease have come, in the main, from studies upon pneumonia as it has occurred and spread in more or less circumscribed localities—as in army and contract camps, in hospital wards, asylums and the like; though I am aware it has at times taken a much wider scope. In these instances the designation epidemic appears to be entirely appropriate. But when we view the disease as it occurs among the population at large, we get a very different impression. If its occurrence be expressed graphically the resulting curves suggest more the irregular fluctuations in an ubiquitous, endemic disease than of epidemic outbreaks. It is my belief therefore that such studies as may shed light upon the endemicity of pneumonia may be more enlightening than those directed to its epidemicity.

Almost the first difficulty encountered in such a study is that we do not know precisely what is meant by the term, "Pneumonia," as the word appears in the majority of available statistical records. Is the word used generically, that is, to include all acute inflammations of the lungs? Does it mean the typical lobar pneu-

* Read before the Philadelphia County Medical Society, January 28, 1925.

monia or the broncho-pneumonia? Or does it mean those inflammatory conditions of the lung substance, often fatal, that follow the invasion of the lungs by microbes not ordinarily associated in our minds with the disease pneumonia? Are we to regard these various lung conditions as disease entities of manifold origins or only as secondary processes engrafted upon a specific primary infective process the existence, nature and exciting cause of which are as yet unknown?

From the present knowledge and records none of these questions can be answered satisfactorily. The result is that we cannot approach an analysis of this subject with the same degree of confidence as would be the case were we discussing such definite phenomena, as are manifested by the notoriously epidemic maladies, cholera, typhoid, plague and so forth.

From this I think you will appreciate that at the very threshold of our inquiry an obstacle presents that may render subsequent steps and conclusions uncertain and fallacious.

We learned much and should have been put securely on our guard by the experiences of the recent tragic pandemic of influenza. I believe I am well within safe limits when I say that a comparatively small number of the fatal pneumonias consequent upon influenza were of the uncomplicated croupous or lobar type—yet they were pneumonia—inflammation of the lung—and often proved fatal and apparently transmissible.

Before one is in a position to speak confidently on the origin of pneumonia it is imperative that a classification of these various manifestations be made. As the matter now stands almost the only deduction that one can make from the published figures is, vague as it may seem, that some, as yet unknown factor predisposes from time to time varying numbers of individuals to inflammation of the thoracic viscera; and that in certain instances these infections group themselves in such a manner, pathologically and clinically, as to suggest a common, specific, exciting cause, while in others they do not.

That the typical frank, lobar or fibrinous pneumonia—the most dramatic picture in clinical medicine—is a definite disease entity no one can at this time doubt—but by no means all pneumonias are of this type and hence a difficulty.

I do not find the task of interpretation much lightened even by a consideration of true lobar pneumonia alone; for when we review the data that we have on that disease we cannot but exclaim: if we are in possession of all the facts concerning the specific etiology of this disease, why is it not possible to do more in either its prevention or its cure, or both? In spite of all that has been done, and well done, and all that we think we know of this disease, the mortality reports show a steady persistence of pneumonia in practically all parts of the country.

I am aware that the doubt here implied as to the sufficiency of our knowledge, is treading on rather sacred ground, yet I cannot avoid the impulse to risk it.

It would be superfluous to detain you with a recital of the prevailing view of the relationship between lobar pneumonia and one or another of the several varieties of pneumococcus always present in the diseased lung. Because of this regular association, the opinion is very general that pneumococcus is the one and only vital factor concerned in true lobar pneumonia. This view is as fixed in the minds of many as was at one time the view that the so-called hog cholera bacillus, always present in the characteristic lesions of that disease, was the cause of hog cholera—yet time has shown that throughout all the careful experimental work on hog cholera we were, for the most part, unconsciously dealing with at least two exciting factors: one, quite obvious, easily recognizable, and readily lending itself to experimental study, the hog cholera bacillus—the other, obscure, evasive, invisible, but apparently ever present, a filterable or ultra virus. The one, the latter, the real cause of the disease; the other, the former, only a regular accompaniment. As a result, years of labor and reams of publications upon hog cholera are today but of historic interest.

Let us consider for a moment some of the work that is based on the belief in an etiological relationship between pneumococcus and pneumonia and forget all else for the time being.

We find that with every case of classical, clinical, lobar pneumonia, pneumococcus of one type or another is always present. There is no room for doubt that it is the agent accountable for the pathological lesions of the lung that characterize the disease. We do not find, however, that recovery from a pneumococcus pneumonia confers immunity from a second invasion, either by the homologous type of pneumococcus or a primary invasion by one or another of the related types. In fact, a primary attack seems in some instances to predispose to subsequent attacks. We find that by following customary immunologic methods serum may be obtained from experimental animals that may exhibit more or less protection to other animals from general infection by the homologous pneumococcus strain. But on man, we also find that the homologous serum obtained from the experimental animal has, as a rule, rather a disappointing influence on pneumonia.

As a result of all this one cannot avoid the suspicion that the problem of pneumonia in man is being approached in a too restricted way. Perhaps more of the effort directed to the prodromes of the disease pneumonia and less to the local lesion and the intimate peculiarities of the pneumococcus accountable for the local lesions, something of greater value to a full understanding of the origin of the disease might result. In making this comment I have no intention of belittling the value of the current experimental activities.

I wish only to convey the idea that I regard their scope as too circumscribed and I believe the work based on the assumption that pneumococcus and pneumococcus alone is the cause of pneumonia has gone far enough to justify the suspicion that some other agent, as yet not identified, may be concerned primarily in exciting the disease; in preparing the way for the lung developments.

This should not be considered as either destructive or retrograde. I have already mentioned the hog cholera experience—that of influenza may properly be recalled to our minds. For years after Pfeiffer introduced us to the organism that bears his name, opinion was pretty well centered upon the Pfeiffer bacillus as the cause of influenza. It was always present in true cases—still is for that matter; it appeared early in the disease and persisted late into convalescence. Experiments demonstrated that one of its characteristics was the elaboration of an intoxicant which when injected into lower animals called forth signs and symptoms strikingly like those seen in man suffering from the disease. It seemed to many that all the postulates needed to establish a causal relationship of that organism to influenza had been reasonably fulfilled—yet we now learn, through the work of Olitzky and Gates—that during the first thirty-six hours of influenza—and not after that time—there is to be found in the exudates from that disease, an organism hitherto unrecognized—differing in many important particulars from the common run of bacteria; which organism they believe to be the primary invader in influenza; playing the role during its early sojourn in the tissues of preparing the way for the later invasion and activities of the Pfeiffer bacillus and the other organisms so commonly seen in influenza.

If one might be permitted to speculate, it seems more than reasonable to suspect that this “preparer” of Olitzky and Gates had been in the tissues for a longer time than thirty-six hours; its invasion probably antedating its disappearance and the advent of recognizable symptoms by many hours; an interval that we may call the incubative time. Also it may be conceived that, as in the case of measles, this primary period, before either disease can be recognized clinically, may be that of highest contagiousity. This view would at once account for the difficulty, yes the impossibility, of preventing dissemination.

I am not unmindful of the impressive experiments of Cecil and Blake on artificially induced pneumonia in monkeys, yet I cannot shake from my mind that we may have gone sufficiently far on the assumption that pneumococcus is the one and only organism concerned in originating the disease pneumonia as we see it in man; and that the lesions of the lungs, vitally important though they be, comprise all that is of moment in the development of this ubiquitous malady.

I believe the time is ripe for the study of pneumonia to be begun

from another viewpoint; a viewpoint that does not regard the local pulmonary conditions as the disease, but rather as a pathological phenomenon engrafted upon a condition that had been excited and prepared by a living germ as yet unidentified.

It is pretty generally agreed that the discovery of the exciting cause of a disease is the first step toward its ultimate eradication. One is forced by this dogma to exclaim: if pneumococcus is the exciting cause of the disease pneumonia why then has so little progress been made in lessening the incidence of pneumonia? Have we in the pneumococcus the real cause of pneumonia or is it only the organism responsible for an outstanding lesion peculiar to the disease? I do not anticipate that this suspicion of a possible dual etiology for pneumonia will be the cause of much astonishment. All through the work on this malady, both clinical and experimental, one frequently encounters the suspicion of the activities of some "unknown factor," some, "determining influence," some, "predisposing cause," and so forth, and it is significant that these expressions convey to me at least, the impression that there is now and then in the minds of those using them not a predisposing influence as the expression ordinarily implies, but rather something vital, more direct, more specific, something, possibly, that is operative either coincident with or anterior to the activities of the pneumococcus, or the streptococcus or whatever other organisms that may be concerned in the pulmonary changes. If these speculations be worthy of consideration it is not inconceivable that the origin of the real disease, pneumonia, not only antedates the lung changes, but may coincide with the invasion of the body by a totally different parasite from those commonly and easily found in the various pulmonary phenomena that accompany the disease later on. At one time these secondary local lesions may be those of the true fibrinous, lobar inflammation from which lobar pneumonia takes its name; and which are due to the activities of pneumococci; at other times the engrafted lung lesions may be of the bronchial type, commonly following influenza, and arise from the invasion by one or another variety of streptococci; at still others, from one or more diverse organisms singly or together, that are not usually associated in our minds with the disease pneumonia. Sometimes sharp etiological distinctions for the lung lesions are difficult to make. Whether these doubts upon the sufficiency of our knowledge of the real cause of pneumonia are worth more than passing notice cannot be decided, as they are not based upon any convincing experimental data; but even so, it is highly desirable that experimental inquiry be directed to something other than the lung conditions seen in the various manifestations of the disease we call pneumonia.

From the vast amount of work that has been done on this puzzling disease, what is it possible for us to glean that is of value in enlightening us upon the reasons for its endemicity and its occasional epidemicity? From my standpoint, very little.

There are no good grounds for doubting that the organisms accountable for the characteristic pathology of pneumonia gain access to the lungs by way of either the mouth or nose, and should the future reveal the presence of some additional organism as yet unknown that may serve to prepare the way for the commonly present pneumococci and streptococci—it may be predicted that that questionable organism will be found to have the same portal of entry. In any event and obviously the transmission of the disease is to be prevented by making impossible the transference of materials from the oral and nasal cavities of the sick to those of others in the neighborhood.

I have no doubt that those of you who have studied in detail the immunologic reactions of the various types of pneumococcus will be astonished when I say I am by no means convinced that the pneumococcus commonly present in the mouth cavity as a commensal is so fixed in its innocent qualities that it may be dismissed with little or no consideration. Nor am I of the opinion that we are as yet in a position to conclude that, under as yet unknown influences, it may not acquire dangerous characters, all immunologic arguments to the contrary, notwithstanding; especially if coincident with or antedating its entry into the lung, the resistance of the tissues has been reduced through the activities of some other as yet unidentified microbe. I am quite certain that this suggestion will be received with many reservations, because of the fixity and almost universality of the belief in the nontransmutability of the various types of pneumococcus. Remember please that the types of pneumococci are not immutable species—they are but varieties of one and the same original species; they have evolved presumably through environmental influences which are as yet unknown to us; and remember too that the characters by which these various types are distinguished the one from the other are not structural, that is morphologic, but are functional, that is physiologic, a distinction of very great moment to an understanding of their relationship.

If, through environment with which we are not acquainted, these four or five types, with their countless subvariations can evolve, is it inconceivable that by analogous influences the usually harmless commensal variety may acquire dangerous characters; either through changes within itself or through association with some other organism, either symbiotically or in sequence? Taking the matter in the reverse order—it is a common observation that the highly virulent pneumococci present in the lungs during pneumonia frequently become less and less virulent as convalescence proceeds until they often become almost devoid of that property; especially when they reach the upper air passages. We see then that under natural surroundings virulence is variable and by no means a fixed quality. It is not at all an uncommon observation that persons

in attendance on patients ill of pneumonia often have in the upper air passages pneumococci of the same type as that in the lungs of the patient; yet the attendants, with a few exceptions, escape pneumonia; and what is of equal interest, the virulent pneumococci usually disappear completely or they gradually assume the pathogenic characters of the lowly virulent or harmless type.

Whether the various accepted types of pneumococci persist as distinctly pathogenic potentials or not, the practical fact remains that they are found in the normal mouth or in the diseased body only; the human being must therefore be regarded as the transmitting agent, the focus of possible danger.

At first glance all this seems to simplify the matter very much—but does it? Not to my mind. Would we be justified, in view of what we know of the ubiquity of pneumococci among normal human beings, in separating from their fellows all persons known to harbor this organism, or, accepting the type doctrine, could we identify and isolate all persons known to harbor those types commonly present in the pneumonic lung—or again would it, in the present state of our knowledge, be advisable to do so?

If it is conceivable that a systemic condition antedates the lung expressions seen in a fully developed case of pneumonia, and is caused by a vital agent as yet undiscovered, may we not have at least a speculative explanation for the transmission and ever presence of the malady? Certainly no such explanation is afforded by studies thus far made on the assumption that pneumococcus causes the disease. May not the disease be most transmissible during its earliest, incubative stage, a time during which pneumonia as we know the disease is not in evidence? May we not from this viewpoint make at least one step toward a visualization of its endemicity, so important to an understanding of its epidemicity?

A very widespread opinion relating to the origin of pneumonia is that "common colds" (whatever that expression may comprehend) are often the precursor. So general indeed is this belief that one is forced to regard it as in part at least sound. What are the processes in common cold that may invite the advent of pneumonia? Up to the impressive experiments of Cecil and Blake—mentioned above—practically all of the experimental efforts to produce pneumonia in animals were predicated on the idea that in one manner or another the tissues of the lungs required to be prepared, before the pneumococci could proceed to elaborate the typical pneumonic lesion. Such preparation—the details need not be gone into here—aimed to interfere at various points in the lung with its normal function—either by shutting off lobules, plugging up bronchioles, or interfering with the local blood supply. Does not some or all of this occur in varying degree in common cold with the lung involvement that so often accompanies it?

What is it in the common cold that may function as the preparing

agent? Is it the ordinary organisms of the mouth or nose or those of the upper pharynx, or the filterable viruses to which attention has been directed in recent times, or is it the mechanical obstruction afforded by the accompanying catarrhal conditions? Possibly one, possibly all, but a certain reply cannot be made, for common colds have not as yet been subjected to the degree of experimental scrutiny that their importance demands.

Then again: if we consider measles; it is not measles alone that causes anxiety but the possible bronchopneumonia that so often follows it. During the past few years our notions of this disease have undergone some very radical revisions; as a result of which we now maintain that measles is at its highest stage of contagiousity before it can certainly be recognized as measles. That is to say—it is most contagious during the prodromes when it is often indistinguishable from a common cold. There does not exist the least evidence, either experimental or clinical, that measles and common colds are in any way related, yet in their earliest stages they are clinically indistinguishable from one another and in their later stages both often lead to inflammation of the thoracic viscera.

It is just such considerations as these that force me to wonder if we have derived through experimental effort thus far made, all that we should have for a correct interpretation of the various pneumonias, or for a sound understanding of the endemicity and occasional epidemicity of the disease.

From the foregoing considerations it is obviously impossible to make dogmatic statements concerning the important phases of this puzzling clinical and epidemiological riddle.

After all the work that has been done on pneumonia there is scarcely an infective disease in which so little progress has been made in the way of its prevention.

It is not necessary for me to take your time in reciting that which is to be found in every modern text book on the general questions of transmission and prophylaxis. It is all based on the assumption that transmission is by way of matters ejected from the lungs, and that pneumococcus is the one and only factor to be considered. I have called that latter view into question with the hope that future investigations of pneumonia may depart from the beaten track and approach the problem through a new avenue.

Conclusions. The evidence does not justify the belief that the endemicity and occasional epidemicity of the disease pneumonia are due to the simple transference of one or another of the types of pneumococcus from the sick to the well.

The fact that recovery from pneumonia confers no appreciable immunity from subsequent invasions by the homologous type of pneumococcus (or by other types) justifies a question as to the etiological relationship of that organism to the disease pneumonia.

The occurrence of pneumonia as a result of the activities of

diverse organisms suggests the possibility that the lesions of the lungs are but secondary to an antecedent general or local condition brought about by some other as yet unidentified organism.

If the pulmonary lesions may be regarded as secondary developments, may not the spread of the disease be explained by the existence of some, as yet unknown, predisposing agent; and may not invasion and transmission occur before the disease is recognizable as pneumonia? This would explain the persistent, ubiquitous, high rate of morbidity as well as the occasional epidemic explosions.

THE SIMULATION OF ACUTE RESPIRATORY DISEASES BY SECONDARY LUNG TUMORS.

By LLOYD F. CRAVER, M.D.,
THE MEMORIAL HOSPITAL, NEW YORK CITY.

MALIGNANT tumors hold today more interest than ever before, chiefly, probably, because of our increased therapeutic resources. One result of this increased interest is that these cases are now subjected to much more searching scrutiny, because with possession of several modes of treatment it becomes necessary to analyze each case individually, in order properly to judge which form of treatment is most suitable. For example, in dealing today with mammary cancer the surgeon feels that it is extremely important to know whether a slight cough, perhaps scarcely noticed by the patient, is a symptom of pulmonary metastasis, or whether a slight pain in the pelvis means bone metastasis. The writer has called attention¹ to the fact that for the early detection of pulmonary metastases physical signs, as well as the roentgen-ray, have a distinct value, and that in some instances physical signs are present before the appearance of symptoms, as stated by Roberts and Perkins,² and sometimes, apparently, before the roentgen-ray plate shows any abnormality. Manges³ has also stressed the need for careful physical examination, instead of relying entirely on roentgen-ray examination.

In observing the course of cases of pulmonary metastasis several instances have come to our attention in which an acute respiratory disease has been closely simulated, in some cases even leading at first to errors in diagnosis. It is quite common for patients who have just developed evidence of pulmonary metastasis to say that they have recently caught cold, meaning usually that they have had a cough for two, three or four weeks, accompanied perhaps at the onset with malaise, chilliness and indefinite pains in the chest. Such cases are mentioned by Stokes,⁴ Holt and Rattermann⁵ and Robey.⁶ Burt⁷ cites a case of secondary spindle-cell sarcoma in

which, six months after removal of a tumor from the forearm, there was a sudden onset of pain in the right side of the chest and inability to get out of bed, followed in one week by shortness of breath, and in five weeks by death. Oliver⁸ describes the sudden appearance of cough, pain in chest and dyspnea simultaneously with pains in extremities, heralding the coincident development of hypertrophic pulmonary osteoarthropathy and metastatic sarcoma of the lung.

There is, however, a distinct group of cases in which the onset and course of the pulmonary metastasis is much more stormy, so much so that, depending upon the symptom complex, a diagnosis of lobar or bronchopneumonia, acute pleurisy, empyema, tuberculous phthisis or acute miliary tuberculosis may be erroneously made. Acute miliary carcinosis or generalized pulmonary cancerous lymphangitis of the lungs in young subjects suffering from gastric carcinoma which may give no stomach symptoms has been described by Beger,⁹ Bard,¹⁰ Sternberg¹¹ and others. Empyema was simulated in a case of sarcoma (primary in lung?) described by Rolleston and Trevor.¹² Marfan,¹³ in 1893, in Charcot's *Traité de médecine*, under clinical forms of cancer of the lung, speaks of "cancer pleuropulmonaire aigu ou galopant," and cites the observations of Bucquoy, Duguët, Jaccoud, Hérard and Cornil in similar acute cases, but omits bibliographical references. Bard¹⁴ quotes Marfan's description of the clinical picture as follows: "The disease, primary or secondary, develops with an astounding rapidity. In the midst of perfect health the patient begins to cough, exhibits an excessive dyspnea and dies in a month with progressive asphyxia; the diagnosis most frequently made is acute phthisis." Simulation of bronchitis, pneumonia, tuberculous phthisis or acute tuberculosis, and particularly caseous pneumonia affecting chiefly the base, as well as of pleural effusion or empyema is described by Roberts and Perkins.² Osler¹⁵ gives brief mention to the "acute galloping pleuropneumonic form."

Several examples are found in the literature of simulation of pneumonia by secondary lung tumors. It may be that in many of these cases true pneumonia has been present in addition to the metastatic tumors. Burt⁷ says: "As the tumor grows, reactive inflammation is apt to be set up, and in the lung the inflammation is usually catarrhal." Tyson and Fussell¹⁶ speak of reactive pneumonia in tumors of lung as being the probable explanation of the time-honored symptom of prune-juice sputum, and also of the fever in these cases. On the other hand, Hellendall¹⁷ thought that in his case the fibrinous pneumonia was an intercurrent affection, and prepared the soil for the growth of the metastases. In this case one and a half months following removal of a fibromyxosarcoma from the buttock a typical attack of pneumonia occurred, the temperature reaching 40.4° C., and a crisis occurring on the

tenth day. Following the crisis, however, the patient failed to recover, and showed symptoms and signs which were thought to be due to a postpneumonic phthisis, death ensuing one and a half months after onset of the pneumonia. Autopsy showed extensive secondary deposit of a tumor in the lungs identical in structure with that which had been removed from the buttoek.

Others who have directed attention to symptoms suggestive of pneumonia in cases of rapid dissemination of secondary tumors in the lungs are Fowler and Godlee,¹⁸ Martin,¹⁹ Mix²⁰ and Sternberg.¹¹ Mix's patient had had a breast removed for carcinoma, and an operation for recurrence, yet a diagnosis of pneumonia was made, a blood culture was reported positive for pneumococcus and a great deal of laboratory investigation was made. To Mix the significant feature of the physical signs was that breath sounds were for the most part absent over the bases despite the presence of marked dulness. His comment seems justified: "When one approaches a patient who has had carcinoma of the breast, with a recurring nodule which has been removed by a surgeon, attention should at once be directed to possible carcinoma metastases. If you go into a field in which wheat has been sowed you expect to find wheat, and if you investigate a patient who has had carcinoma and who is sick, you will expect to find carcinoma metastasis. In such a case one ought not to look for Bright's disease, and make elaborate blood and urine chemical tests or immediately start making blood cultures; one should rather first examine the patient, and then having found out what the patient shows on physical examination, should at once direct investigative work toward these findings."

That acute pleurisy is often simulated by metastatic pulmonary growths was noted by Laennec²¹ (cited by Unverricht,²² who also quotes Trousseau as stating in his *Leçons de clinique médicale* that we possess no reliable symptom which puts us in a position to recognize the nature of the disease—pleural effusion). Dieulafoy²³ says: "Hemorrhagic pleurisy in cancer may arise quite suddenly, like acute pleurisy. . . ." Montel and Hauvuy²⁴ have recently reported a case in which sarcoma of the thigh had been developing for four or five months without attracting attention, and in which suddenly dyspnea from a hemorrhagic purulent pleural effusion appeared and proved rapidly fatal.

Acute miliary tuberculosis was so closely simulated in a case of Zinn,²⁵ a pregnant woman, aged thirty-one years, with a chorio-epithelioma, that an erroneous diagnosis was made. The clinical picture was at first dominated by marked dyspnea and cyanosis, together with hemoptysis and frequent vomiting. After a few days there was a sudden attack of extreme shortness of breath, cyanosis, fever (38.3° C.) and diffuse capillary bronchitis.

This paper deals only with secondary lung tumors, but it may not

be out of place to mention at this point that the acute onset also occurs in primary lung tumors, as stated by Marfan,¹³ Pässler²⁶ and others.

Case Reports. The following cases have come under observation at Memorial Hospital since January, 1923. For the sake of brevity only the pertinent facts of each history are given.

CASE I.—A. McK., a white girl, aged seventeen years, suffered from periosteal osteogenic sarcoma of the lower end of the right femur, for which she had been admitted, October 29, 1923. She had had a series of roentgen-ray treatments.

On November 3, 1923, a roentgen-ray plate of the chest was negative for metastases.

On November 25, 1923, her temperature suddenly rose to 103° F., and there was marked shortness of breath, pain in the right side of the chest and some cough, but no expectoration. The house surgeon after examination of her chest said that he thought she had pneumonia. However, on the next day, November 26, the signs were those of a large pleural effusion on the right side, with a temperature of 104° F.; pulse, 144; respirations, 34. It was felt that the chances were that the illness was due to pulmonary metastasis with unusually severe reaction and pleural effusion. Thoracentesis obtained 14 ounces of blood-tinged fluid. There was a leukocytosis of 16,000. The next day, November 27, the temperature had fallen to 102° F., and she felt better.

On December 7, 1923, a roentgen-ray plate of the chest showed evidence of metastases.

The patient continued to have a slight fever, the temperature fluctuating between 98.5° and 101° F., finally subsiding by lysis after thirty-one days.

Examination of the lungs on December 13 showed the following: Flatness, with absent or greatly diminished breath sounds and tactile fremitus at right base posteriorly and laterally. Over right base anteriorly decreased breathing and crackling and sonorous rales. Some decrease of breath sounds with faint crackling rales at left base laterally. Diagnosis: Metastasis to lungs; probably less fluid than before.

On December 31, 1923, roentgen-ray plate of chest: "Previous report confirmed; sarcoma metastasis. Deposits throughout right side" (Fig. 1).

The patient died, February 9, 1924, at home, a little over two months following the onset of the lung symptoms.

CASE II.—G. H. W. a white man, aged forty-seven years, who had developed a small sore on the lower lip about two years before and who had been treated elsewhere for one year by various measures, including high frequency electric current, violet-ray, cautery,

roentgen-ray and excision of the lip tumor, under a clinical diagnosis of "skin cancer." Treatment had been continued at Memorial Hospital with radium, also under a clinical diagnosis of carcinoma of the lip. However, tissue removed from the left submaxillary region on April 23, 1923, in the course of a submaxillary dissection was reported as showing a "large spindle-cell fibrosarcoma of neurogenic type."

When the patient was seen on March 28, 1924, he had been readmitted with a note that he had recovered from an attack of pneumonia at his home about six weeks before, and that his general condition was as a result somewhat below normal. There was still a non-ulcerated plaque of tumor tissue in the musculature of the chin $3\frac{1}{2}$ by 2 by $\frac{1}{2}$ cm.

Examination of the patient on March 28, 1924, revealed dulness with diminished breathing and a few crackling rales, together with some change in voice sounds at the right base. Similar changes, but less marked, were also present in the left interscapular region. There was a soft subcutaneous nodule on the left chest wall, a soft lump over the spine of the right scapula and another lump, possibly a lipoma, over the lumbar region. (The first two lumps resembled neurofibromas in their consistence.)

As the case was still being treated under a clinical diagnosis of carcinoma of the lip, the marked discrepancy between this and the pathological report raised the question whether slides might not have been mixed in the laboratory. However, the signs described above were consistent with pulmonary metastasis, and if the patient really had neurogenic sarcoma of the lip (a rare tumor) there was more reason to fear lung metastasis than there would be if he had carcinoma of the lip. Therefore the following comment was made: "Signs may indicate a residuum of a pneumonia, but if the pathological report of neurosarcoma refers to this case, question of lung metastasis should be investigated further, and I would suggest getting a roentgen-ray plate." It was felt, too, that the presence of the subcutaneous nodules having a consistence like that of neurofibromas tended to confirm a diagnosis of neurogenic sarcoma, because a certain proportion of cases of neurofibromatosis develop sarcoma.

On March 31, 1924, a roentgen-ray plate of the chest revealed "evidence of sarcoma metastases."

The patient was discharged on April 2, and died, May 3, 1924, a little over two and a half months after the onset of his supposed pneumonia.

CASE III.—Mrs. C. R., a white woman, aged thirty-five years, had been treated at Memorial Hospital since January 2, 1924, for carcinoma of the cervix. (Pathological report: Plexiform epithelioma.)

Right

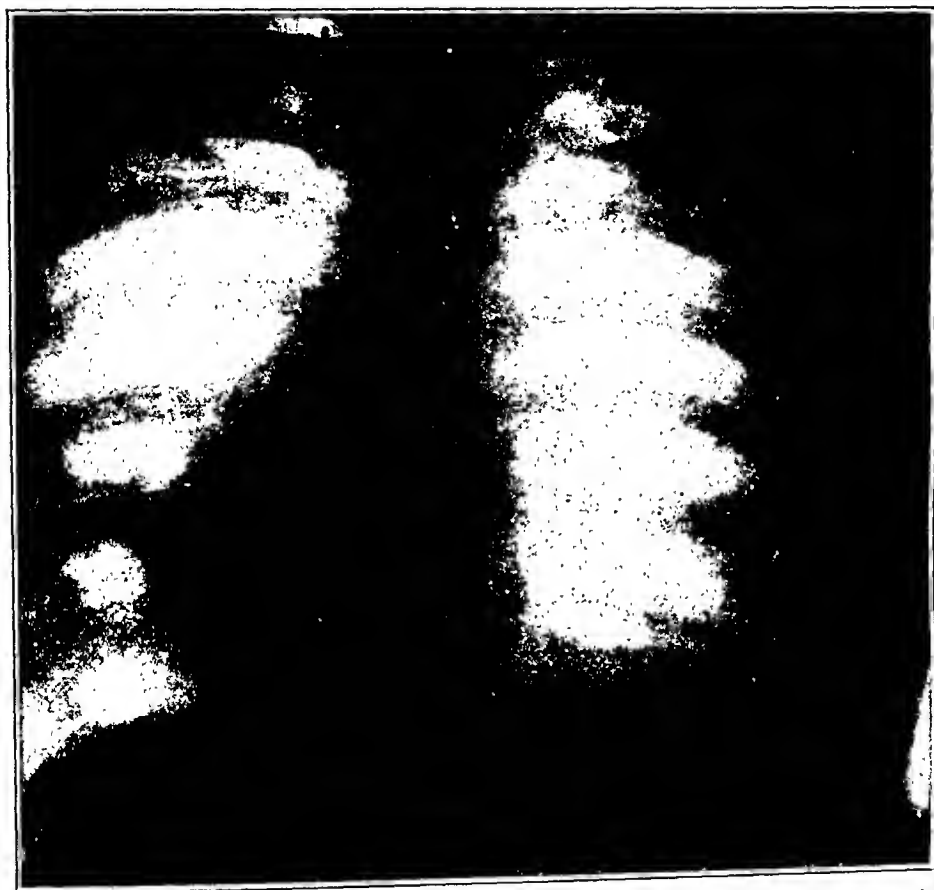


FIG. 1.—Case I. Roentgen-ray plate made, December 31, 1923, confirming the finding of evidence of sarcoma metastases in the previous plate of December 7, 1923.



Right

FIG. 2.—Case II. Plate taken, March 31, 1924, revealed evidence of sarcoma metastases.



Right

FIG. 3.—Case III. Plate made, June 19, 1924, showing numerous discrete circular dense shadows in the bases, also peribronchial infiltration throughout the lungs, most marked on the right. Patient died in less than three months afterward, suffering from pulmonary and pleural symptoms.

The writer was asked to see her on June 20, 1924, on account of a severe cough and pain in her chest. The history with respect to her lung condition was as follows: Her mother had died twenty-four years before of tuberculosis. No other member of the patient's immediate family had ever had tuberculosis, to the best of her knowledge. She had had no miscarriages. Five years before, during the influenza epidemic, she had had pneumonia, with complete recovery, and no subsequent cough. Her present pulmonary complaint began about March, 1924 (three months previously), and first appeared in the form of a persistent cough. There was expectoration of "phlegm," but no hemoptysis. Four weeks before there was a *sudden onset* of "pleurisy" without any history of exposure; the symptoms had been pain in the *right* chest, with a temperature of 102° F. The fever lasted two days. She was in bed one week. When the writer examined her, on June 20, she complained of continual severe cough and of having had a severe pain in her *left* chest posteriorly for the past three days.

The examination of her chest showed marked diminution of breath sounds at the bases all around, and in fact over the lower one-half or two-thirds of each lung posteriorly, without definite changes in the percussion note, tactile fremitus or voice sounds. Occasionally a faint crackling rale was heard at either base. Sibilant rales were heard high up in the left axilla. Slight changes in breath sounds were heard over the left upper lobe anteriorly. Her general appearance was good. From the history and physical signs a diagnosis of metastasis to the lungs was ventured.

A roentgen-ray plate of the chest made at the same time was reported as follows: "Chest plate reveals the presence of multiple rather discrete circular dense shadows in the bases, with evidence of peribronchial infiltration throughout the lungs, most marked in the right, with considerable thickening of pleura. Probably metastases, although bronchopneumonia or miliary tuberculosis should be excluded clinically" (Fig. 3).

The writer felt that bronchopneumonia and miliary tuberculosis could be excluded clinically, considering all the features of the history and the physical examination. It might be noted here that neither during this admission nor during her stay at the hospital in January had she shown any fever, and her pulse and respiratory rate were normal.

She was discharged, June 21, 1924. The next note on her chart is that she was reported on September 5, 1924, as being very ill and confined to bed at home under the care of her family physician for "pleurisy." Sometime between then and September 22 it was reported that she had died.

Discussion and Conclusions. With closer observation of the course of cases of pulmonary metastasis and more careful analysis of their history, we are beginning to feel that a considerable proportion of

these cases have a more or less acute onset, varying all the way from simulation of mild bronchitis or pleurisy to the most severe forms of acute respiratory disease. Unfortunately, the actual onset of the respiratory symptoms is not often observed by those who are concerned with the primary tumor. In many cases no physician is consulted at the onset, especially if it is comparatively mild. In other cases in which the onset is more stormy the family physician or some general practitioner who is not fully cognizant of the existence or the potentialities of the primary tumor may be called, and under the stress of the urgent need for treatment both physician and patient may overlook the importance of the history of a malignant tumor. Moreover, in view of our experience, it seems justifiable to say that, although the simulation of acute respiratory diseases by secondary lung tumors has been described by several writers, its description has found its way into comparatively few text-books, and it does not seem that the profession at large is sufficiently on its guard against this infrequent yet important source of diagnostic and prognostic error. The diagnosis is, of course, much more difficult when the primary tumor is concealed, but if the possibility were always kept in mind that any case with acute respiratory symptoms may be suffering from pulmonary metastases of some malignant tumor (or, for that matter, a primary lung tumor), the chances of error would be much less.

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CILARY INHIBITION OR DESTRUCTION IN TRACHEO-BRONCHIAL ASTHMA, WITH NOTES ON BRONCHOSCOPIC TREATMENT.

BY WILLIAM F. MOORE, M.D.,

BRONCHOSCOPIST, DEPARTMENT OF DISEASES OF CHEST, JEFFERSON HOSPITAL,
PHILADELPHIA.

THE object of this paper is to present results of bronchoscopic, histologic and bacteriologic studies in a series of cases from the Bronchoscopic Clinic of the Jefferson Medical College Hospital of Philadelphia. The majority of these cases are of many years' duration and marked severity. Many have been studied thoroughly in the other special clinics of the hospital.

Theories as to the causative factors which are thought to produce attacks of tracheobronchial asthma are legion, and time and space do not permit of their enumeration. One is impressed on reviewing the clinical material, and on bronchoscopic examination, with the fact that more than one cause underlies this condition.

The speedy relief afforded the great majority of our cases has led us to believe that bronchoscopy alone, affording as it does a means of cleansing the overloaded mucous membrane of the tracheobronchial tree, temporarily alleviates the symptoms and yields relatively permanent results in many cases. This would seem to justify the conclusion that defective ciliary drainage is a factor of the utmost importance.^{1, 2}

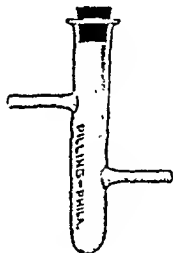
The question as to whether infection of the bronchi is primary or secondary is one of great importance, but difficult of solution. Our help in this must come from the internist and specialist who can point out the possible source. Primary cases have responded

permanently to this form of treatment; secondary cases require, of course, eradication of, or treatment at, the source.

Technic. Asthmatic patients referred for diagnostic bronchoscopy and treatment are first given a complete physical examination by the internist. Roentgen-ray studies are then made. As the majority of these cases have come through the asthma clinic, sensitization tests have been completed. No patient is bronchoscoped without having had a physical examination and roentgen-ray studies.

At the first examination morphin is generally administered hypodermically in doses of from $\frac{1}{8}$ to $\frac{1}{4}$ gr. one hour before bronchoscopy. No general anesthetic has ever been found necessary. In children no cocain is used, but in adults a 10 per cent solution is applied deep enough in the pharynx to inhibit the function of the superior laryngeal nerve.³ This is applied by means of a swab on a curved applicator forceps and repeated once.

There is no contraindication to a bronchoscopic examination during an asthmatic attack in the type of cases herein referred to. Preliminary medical examination has usually eliminated so-called "cardiac asthma" and other conditions in which there is no indication for bronchoscopy.



Collection tube for aspirated material.

Bacteriologic Specimens. Specimens are obtained bronchoscopically, uncontaminated by oral secretion, by two means: Either by swab or, where the secretion is not too viscid and is susceptible of aspiration, it is drawn into specially devised tubes which are inserted between the aspirating bronchoscope and the rubber tube from the suction pump. The tubes are sealed for laboratory examination later. Specimens are immediately "planted" on human blood agar-agar and slide smears made by Dr. George R. Moffitt, one of the group, who will present the results of his work in another paper.⁴ An abstract of some phases of his work is given in a subsequent paragraph.

Bronchoscopic Treatment. Two methods are employed to rid the mucous membranes of the trachea or bronchi of their overload of secretion, namely, sponging where the secretion is thick and tenacious or by aspiration, either through the special aspirating bronchoscope or with a separate aspirating tube inserted through and beyond the bronchoscope. Forceps are ordinarily not required for

this. A solution containing 10 drops of a 10 per cent solution of cocain and 20 drops of adrenalin solution (1 to 1000) in 1 fluid-ounce of normal saline as a vehicle is then instilled, using 5-cc in each main stem bronchus. A 10 per cent solution of silver nitrate has been applied to localized areas in certain cases and in others guaiacol in 5 per cent and gomenol in 20 per cent strength have been used. However, the adrenalin-cocain combination above mentioned, which we know as the "asthma solution," is the one most frequently employed.

Admission to hospital is not required, and the number and frequency of treatments generally depends, after the first two bronchoscopies, on the character and frequency of the asthmatic attacks; the patient being instructed to report at weekly intervals, so that accurate data may be kept. Some patients require but three or four bronchoscopic treatments, while others have needed as many as eighteen.

Vaccines. One week after the diagnostic bronchoscopy (at which specimens are taken) the autogenous vaccine is ready for administration. This is given at four-day intervals in ascending dosage, as outlined by Dr. Moffitt. This part of the treatment is either carried out by the physician referring the case, or the patient returns to the asthma clinic for its administration.

Bacteriology and Vaccines. Among the various organisms the *Streptococcus viridans*, *Streptococcus hemolyticus* or a hemolytic strain of the *Staphylococcus aureus*, in pure culture or associated, are conspicuously present in nearly all cases of asthma. Their role may be (a) causative factors, or (b) secondary invaders responsible for a primary bronchitis upon which the asthma develops. It is reasonable to believe, and this belief is supported by our results, that the use of autogenous vaccines prepared from the organisms found would give promise of establishing, as permanent, the relative cures which have been effected by local treatment, especially by the assistance of ciliary drainage to be accomplished by bronchoscopic aspirations.

The organisms recovered from the secretions of asthmatics, removed by the bronchoscope without oral contamination, show a marked degree of attenuation, which may account for the non-occurrence of metastatic infection. This does not, however, render vaccines prepared from them less potent, for loss of virulence of an organism does not, in any way, affect the efficiency of the vaccine.

Classification of Cases. From the standpoint of results obtained it has seemed logical to assume that the twenty-seven cases herein reported should be grouped in a broad, but convenient, classification, as: (1) Those with bronchoscopically evident active suppurative tracheobronchitis;¹ (2) those with a bronchoscopically evident chronic passive congestion. In the first group are placed

all those showing an inflammatory mucosa with a great deal of secretion. In the latter are placed those cases in which the mucosa has assumed the bluish-red, leathery appearance, with little or no secretion, or those with inspiratory or expiratory collapse of the bronchi, also with little secretion. It has seemed to us that a true infection was responsible for the major (first) division, while in the second group factors outside the tracheobronchial tree were responsible for a continuation of the symptoms; and the local infection, if any, was secondary and played a minor role in causing attacks. We are cognizant of the fact that this division is open to criticism from many angles, and that the borderline is rather hazy in some cases; still it is necessary for workers in this field to have some criteria for classification that may serve as a basis for therapeutic indications from which they may reasonably expect to get results.

TABLE I.

CLASS I.—TRACHEOBRONCHITIS PRESENT.

No.	RESULT.
3	Great improvement; no attacks in eight months.
4	Improved.
5	Improved.
6	Improved.
9	Marked improvement.
10	Improved; no attacks in four months.
11	Improved.
12	Greatly improved.
13	Greatly improved.
14	Improved.
15	Improved.
16	Improved; no attacks in two years.
17	No change.
19	Pansinusitis; referred for diagnostic bronchoscopy only.
20	For diagnostic bronchoscopy only.
21	Attacks decreased in severity and frequency.
22	Improved; one attack in four weeks.
23	Improved; no symptoms for one month before discharge.
26	Improved.
27	For diagnostic bronchoscopy only.

CLASS II.—TRACHEOBRONCHITIS ABSENT.

1	Temporary relief.
2	Temporary relief.
7	No relief; probably due to a postpneumonic suppuration.
8	Unimproved; diagnosis; cardiorenal disease.
18	No change.
24	Temporary relief only.
25	Referred for treatment for pansinusitis.

Reports of Cases. In presenting the following tabulations of cases it will be noted that none has been pronounced cured, although two years have elapsed in one case since having an attack. When a case can be pronounced permanently cured seems justly to be a much mooted question with the internists. It would seem that for

the purposes of determination of the efficiency of treatment a patient free from attacks for a year might be called a relative cure.

Ciliary Movements and Histology of Ciliated Cells. Dr. George R. Moffitt⁴ has made a most interesting and important report of the results of his work with us at the Bronchoscopic Clinic in a paper on the pathologic histology and bacteriology of asthma. With his permission we here present some of his observations which are pertinent to our subject:

"The bronchial columnar epithelial cells are 40 to 50 micra long and 10 to 14 micra in diameter. Together with these cells are ciliated spherical cells which do not appear to be the goblet cells that are normally present in the bronchial mucosa.

"There are as many as 480 cilia attached to a cell. Works on histology have given the number as 12 to 25. The ciliary movements are at the rate of 360 a minute or 6 a second. There is a secondary ciliary movement which forces secretion and foreign particles from the bronchial wall into the lumen. The cilia are 18 to 20 micra long. The only reference found upon this subject gives 3 to 5 micra as their length.

"The basal or root process (not mentioned by any treatise on histology) apparently connects the cells of the free edge or uppermost layer to the basement membrane.

"One or more of the following changes occur in the ciliated columnar epithelial cells of the asthmatic: (1) Loss of the ciliary motion which produces a current; (2) complete loss of ciliary motion; (3) actual loss of the cilia; (4) fatty degeneration of the cell.

"Regeneration of Ciliated Epithelium. The question arises as to the character of regeneration of the destroyed epithelial cells and repair of the injured bronchial mucous membrane. It is a well-known pathologic fact that mucous membrane, in general, regenerates more rapidly and more perfectly than any other tissue. At the same time it is uncertain as to whether a cell from which the cilia have been removed by trauma or disease could replace those lost processes by new ones.

"There seems to be no reason why this should be considered impossible, and our observations lead us to believe that replacement of cilia or ciliated cells, lost by disease, with new cilia or new ciliated cells does take place. The cilia, as has been stated, are connected with delicate intracellular fibrillæ within the superficial parts of the cell and are in all probability continuous with these fibrillæ, each of which in turn is connected with and controlled by two-minute bodies of centrosomic derivation. It is not inconceivable that when a cilium is lost these bodies may cause the fibrillum to grow and extend beyond the cuticula as a new cilium. This would be a repetition of the process that goes on in each normal nonciliated cell as it reaches the free surface of the stratified layer of cells, for the cells beneath the surface, as has been previously stated, possess no cilia.

TABLE II.

No.	Duration in years.	Solution used.	Appearance.	Secretion.	Bacteria.	Röntgen ray examination.	No. of bronchoscopies.	Result.
1	20	Cocain-adrenalin	Inflamed and velvety; secretion present	Small amount	Str. viridans	Peribronchial thickening; root shadows dense	2	Improved; the symptoms not returned.
2	4	Cocain-adrenalin; 20 per cent gonol	Local inflammation; collapse of post wall	Very little	Thickening at roots and right lower lobe	4	Improved; no return to date.
3	1	Gomenol (20 per cent)	Trachea and right bronchi inflamed; right bronchi dilated	Visible; bronchi and right lung	Str. viridans, B. influenza; Str. hemolyticus	Thickening of roots and left lower lobe	15	Discharged; no symptoms for ten months.
4	9	Cocain-adrenalin	Chronic inflammation of bronchi mucosa; secretion present	Tenacious and scant	Str. viridans; Sta. aureus	Peribronchial thickening of right lower lobe	4	Improved; no return in ten months.
5	9	Cocain-adrenalin	Bluish-red	Small amount	No culture	Dense right upper and middle lobes	5	Improved temporarily only.
6	5	Cocain-adrenalin	Mucosa inflamed	Dry	Root shadows heavy	7	Improved; died of intercurrent disease.
7	15	Argyrol (20 per cent)	Congested and edematous	Thick and adherent	Fibrosis of lower right lung	2	Unimproved.
8	1	Bluish-red	None	No culture	Fibroses of both bases	4	Improved, temporarily only.
9	2½	Gomenol and cocain-adrenalin	Inflamed and grayish-white	Tenacious	Str. viridans; Sta. aureus	Thickening at roots	18	Improved; no attacks for four months.
10	15	Cocain-adrenalin	Injected and bluish-red	Quite viscid	Str. hemolyticus	Few dense lymph glands; no thickening	12	Improved.
11	3	Cocain-adrenalin	Inflamed trachea and bronchi	Present throughout	Slight thickening at roots	..	Improved.
12	2	Cocain-adrenalin and 10 per cent nitrate locally	Bronchial orifices normal	Very thick	Str. viridans; Str. hemolyticus	Thickening at roots	..	Greatly improved.
13	2	Cocain-adrenalin and K. I.	Normal	Thick and viscid, only in middle lobe	No culture	Peribronchial thickening at right lower lobe	16	Improved.

14	2	Cocain-adrenalin	Mucosa injected	Tenacious	Str. viridans	Peribronchial thickening	3	Improved.
15	3	Cocain-adrenalin	Red and injected	Large amount and sticky	Str. viridans; Str. hemolyticus	Thickening at roots	2	Improved.
16	12	Cocain-adrenalin	Red and injected; collapse of posterior wall	Thick and tenacious	Peribronchial thickening	2	No attack in two years.
17	17	Cocain-adrenalin	Trachea and right main stem bronchus inflamed	Thick and tenacious mucopus	No culture	Peribronchial thickening, general, at roots	2	No change.
18	10	Red and inflamed	Gelatinoid Plastic	Thickening at roots; peribronchial thickening	1	No change.
19	..	Cocain-adrenalin	Inflamed and velvety	Elastic	No culture	Peribronchial thickening of both upper lobes	..	For diagnosis only.
20	39	Cocain-adrenalin	Small amount of thin secretion over the trachea and bronchi		Str. viridans		9	Improved; attacks decreased in their frequency.
21	18	Cocain-adrenalin	Patchy area of inflammation	Small amount and tenacious	Sta. aureus (hemolytic)	Peribronchial thickening of right upper and lower lobe	7	Improved; one attack week the treatment was omitted.
22	10	Cocain-adrenalin	Thick and tenacious	Str. viridans; Sta. hemolyticus	Peribronchial fibrosis of upper lobes	17	Discharged to work, and no symptoms since May 7, 1924.
23	4	Cocain-adrenalin and 2 per cent guaicol and 20 per cent gomenol	Mucosa cyanotic and edematous; collapse on expiration	Pus was exuding from all bronchi	Str. viridans; Sta. hemolyticus; M. cinereus	Peribronchial thickening and fibrosis of entire chest	2	Improved
24	5	Cocain-adrenalin	Bluish-red in carinal region	Mucus high in trachea	Thickening at roots	6	Unsatisfactory; improved.
25	Many	Cocain-adrenalin and silver nitrate	Mucosa inflamed and edematous	Thin, mucoid		13	Improved.
26	Many	Cocain-adrenalin and 10 per cent silver nitrate, locally	Inflamed	Thick and tenacious	Sta. aureus (hem.) and M. cinereus	Thickening at roots	1	For diagnosis only.
27	Inflamed and edematous; no marked collapse on expiration	Root structures heavy and fibrosis of left lower, right, middle and lower lobe		

"However, if it is true that lost cilia cannot be replaced by new ones, the general process of repair of the bronchial mucosa would not be long delayed, for the injured surface cells would soon be exfoliated, as are all surface cells of stratified epithelium, squamous or columnar, and their places taken by the underlying cells which would acquire their cilia by the ordinary physiologic process, whatever that may be.

"If the destructive process were deeper than the epithelium, involving the basement membrane and tunica propria, an ulcer would result and the process of repair would involve the formation of granulation tissue, new fibrous tissue and the proliferation of new epithelial cells from the uninjured cells at the edge of such ulcer.

"Deep ulceration, however, as has been repeatedly demonstrated by bronchoseopy and autopsy, does not occur in asthma."

Summary. 1. Practically all cases which have come to us for treatment have shown on roentgenographic study peribronchial thickening to a marked degree in some part of the lung; in some cases general.

2. Those cases associated with a demonstrable tracheobronchitis have responded best to bronchoscopic treatment.

3. Ridding the tracheobronchial mucous membrane of secretion will in itself temporarily benefit all cases.

4. While temporary relief follows these bronchoscopic treatments, permanent relief necessitates intrabronchial medication; the administration of vaccines made from the organism recovered directly from the bronchial secretions; a general attention to hygiene and an abundant diet, the same as for tuberculous patients.

5. Regeneration of the ciliated epithelium occurs very rapidly after the secretion, which as inhibited its action, has been removed either by aspiration or swabbing.

6. Impairment of ciliary action has been conclusively demonstrated. Its restoration is imperative for lasting improvement.

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CHRONIC MEDIASTINITIS.

BY LEILA CHARLTON KNOX, M.D.,

ASSISTANT ATTENDING PHYSICIAN, ST. LUKE'S HOSPITAL, NEW YORK.

MEDIASTINITIS is a condition which, though always mentioned in academic discussions of thoracic disease, rarely assumes any great interest either clinically or pathologically, so much more often are symptoms referable to organs rather than to their supporting tissues. As a cause of death the disease is certainly infrequent, if we include only those cases in which the condition is not associated with a serious lesion of heart, vessels, bronchi or nodes.

Everyone is familiar with the effects of primary or metastatic neoplasms which give rise to thoracic symptoms, but the present paper deals only with a smaller group of cases, unquestionably inflammatory, in which the mediastinal lesion far exceeds both in extent and activity any other manifestation of disease. These cases may usually be differentiated pathologically and clinically from so-called indurative and mediastino-pericarditis, for the latter, while occasionally resulting in great fibrous thickening of the mediastinal tissues, also involves especially the pericardium from which it proceeds.

The condition is probably nearly always due either to tuberculosis or syphilis; but very rarely other agents which produce granulomata, such as the mycoses, may be the excitants, or an interstitial form of Hodgkin's disease may give rise to mediastinal symptoms. These two are unusual. Scarlet fever, measles, and acute rheumatic fever have each been said to have given rise to productive mediastinal lesions, and in these cases it is possible that a streptococcus is the invading organism.

The symptoms are due to compression or invasion of important structures, and therefore may be either anatomical or reflex physiological phenomena. In such a case observations of the underlying lesions may contribute directly to our understanding of clinical symptoms.

Clinical History. The patient was a negro woman, aged twenty-seven years. She was admitted to St. Luke's Hospital on the medical service then in charge of Dr. F. Warner Bishop, to whom I am indebted for the clinical notes.

Upon arrival the patient was thought to be in fair general condition, and a tentative diagnosis of bronchial asthma was made, but the onset of extreme dyspnea shortly showed her to be by no means out of danger, and she died of respiratory failure, less than twenty-four hours after her entrance into the institution. For this reason only a brief history is available, and few pathological examinations had been made. Unfortunately blood for a Wassermann reaction had not been taken.

The history stated that her chief complaint was recurrent attacks of nausea and vomiting, occurring over a period of ten months. The first attack had begun after eating, and was followed by retrosternal pain and wheezing inspiration, with slight hemoptysis. There was no fever, but the patient had been so prostrated as to be unable to work for one week. A similar attack had occurred two months later, and since that time there had been increasing nausea and distaste for certain foods. For one week before her admission there had been frequent vomiting, induced at times even by taking water.

In spite of the predominance of gastric symptoms in this history her chief difficulty when seen by the ambulance physician was extreme dyspnea, and although expiration was labored, inspiration was still more difficult.

The physical examination showed a young colored woman with eccentric, irregular pupils, which reacted sluggishly to light and accommodation. The lungs were resonant and the breath sounds wheezing and asthmatic, with dry sonorous rales throughout, more on the right side. Other physical signs were normal.

The blood count was normal. The urine contained considerable acetone. The systolic blood pressure was 130 mm., but the usual cycle of changes in the sounds could not be detected and no diastolic level could be determined. A provisional diagnosis of bronchial asthma, due to foreign protein sensitization, was considered, although the unequal pupils suggested a syphilitic infection, and the possibility of an aneurysm was kept in mind. The roentgenogram of the thorax, showing the trachea displaced to the left, seemed to confirm this idea (Fig. 1). Death followed the morning after admission, and an autopsy was performed two hours later.

Gross Pathology. At autopsy the positive findings were as follows: inequality of the pupils and pigmented, parchment-like scars on the dorsa of the feet, the legs and the chest. The liver was attached to the diaphragm and the anterior abdominal wall by numerous rather fresh, veil-like, fibrous adhesions. The capsule was slightly thickened and section showed slight changes due to chronic passive congestion. The gall bladder was small, the wall somewhat thickened, and the bile within it inspissated and tenacious. The spleen likewise showed numerous fibrous adhesions to the surface, a thickened capsule, much fibrosis, and very much diminished lymphoid markings. Both kidneys were smaller than normal, the left weighing 75 gm. and the right 100 gm. The capsules were somewhat adherent and there were depressed scars scattered over the surfaces of both. The left ovary contained a small dermoid cyst.

Both lungs were attached at the apices by fibrous adhesions. The right did not reach to the diaphragm, a small quantity of air undoubtedly being present in this pleural cavity, as was indicated

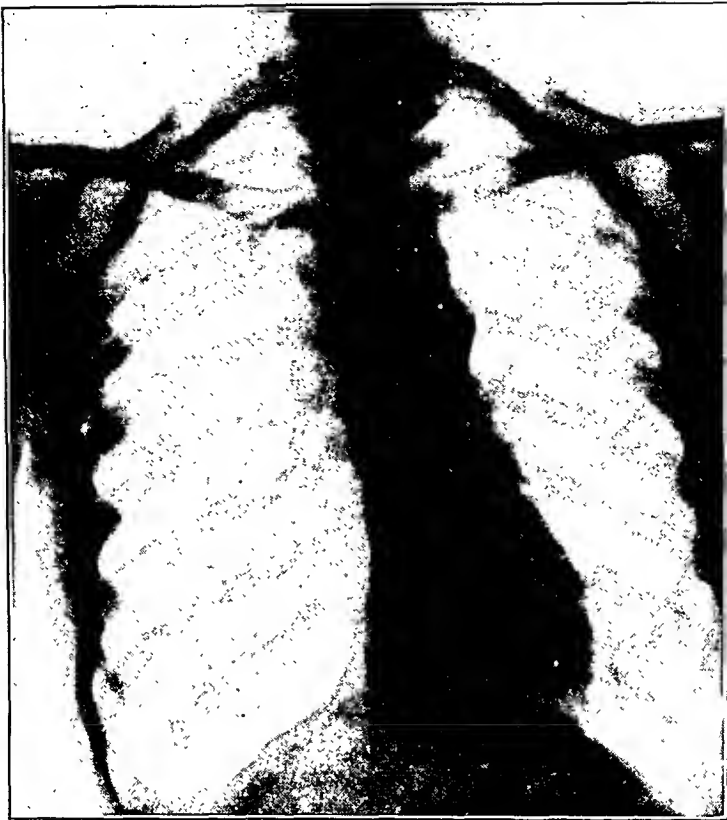


FIG. 1.—Roentgenogram of thorax, showing moderate widening of the mediastinal shadow and the prominent convexity of the aorta which was rotated anteriorly and the trachea displaced to the left. Pneumothorax, right pleural cavity.

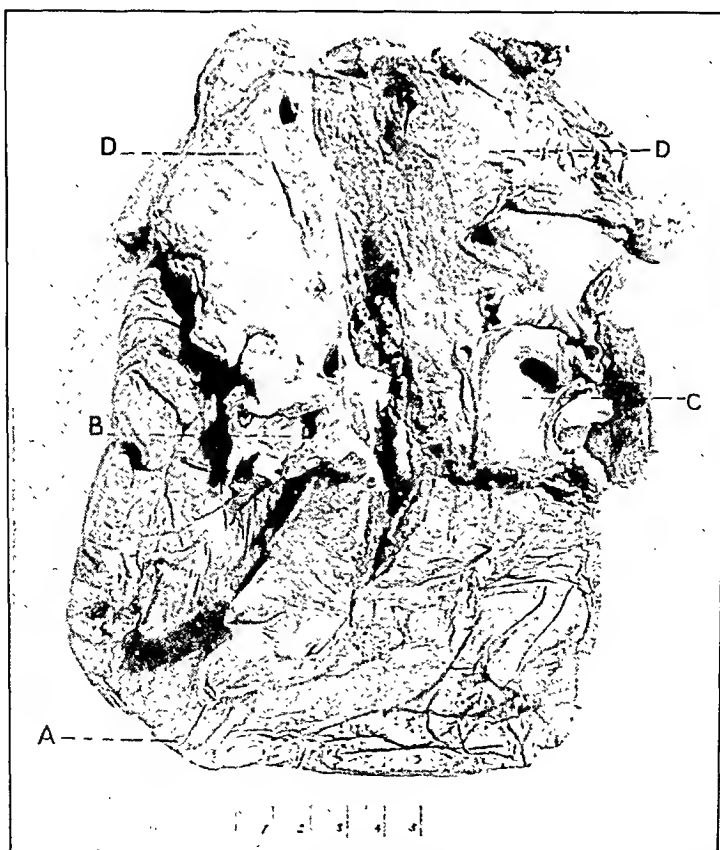


FIG. 2.—Photograph of right lung, aorta and the fibrous mass in the mediastinum surrounding all structures. *a*, Right lung; *b*, right auricle; *c*, ascending aorta; *d*, tumor-like mass in mediastinum.

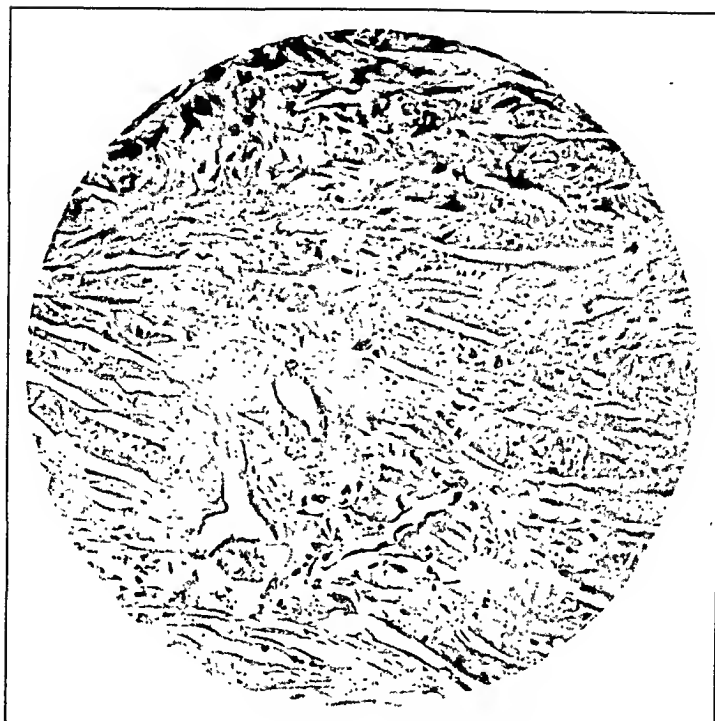


FIG. 3.—Photomicrograph of typical area of the mass, showing the broad keloidal strands of hyaline tissue.

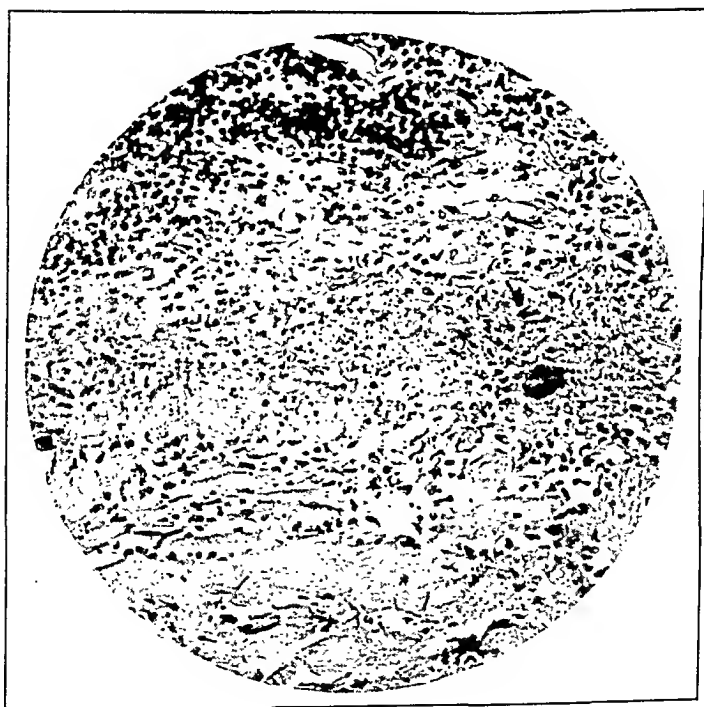


FIG. 4.—Granulomatous area with masses of round cells and necrotic zone with fragmented and pyenotic nuclei.

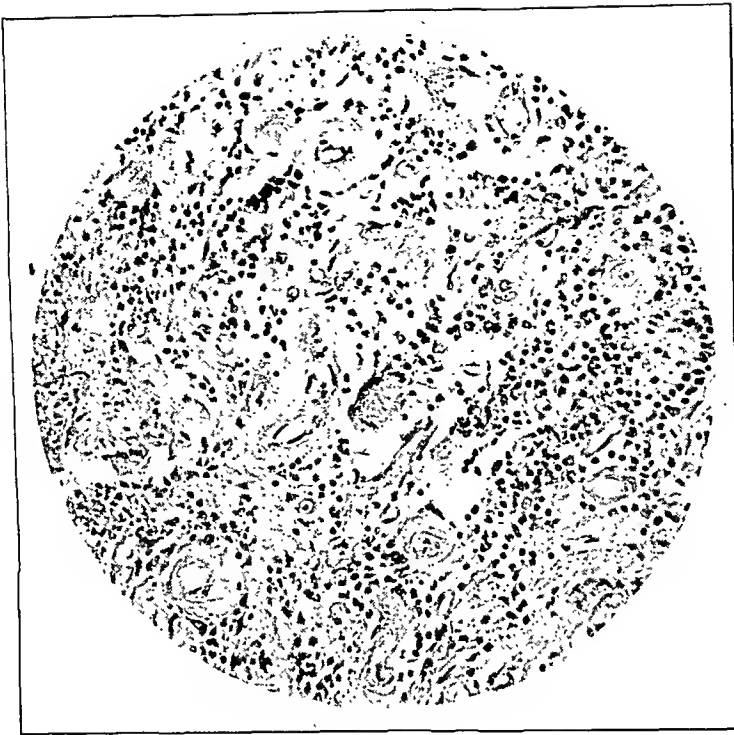


FIG. 5.—Photomicrograph of a vascular field, all the vessels having extremely thick hyaline walls.

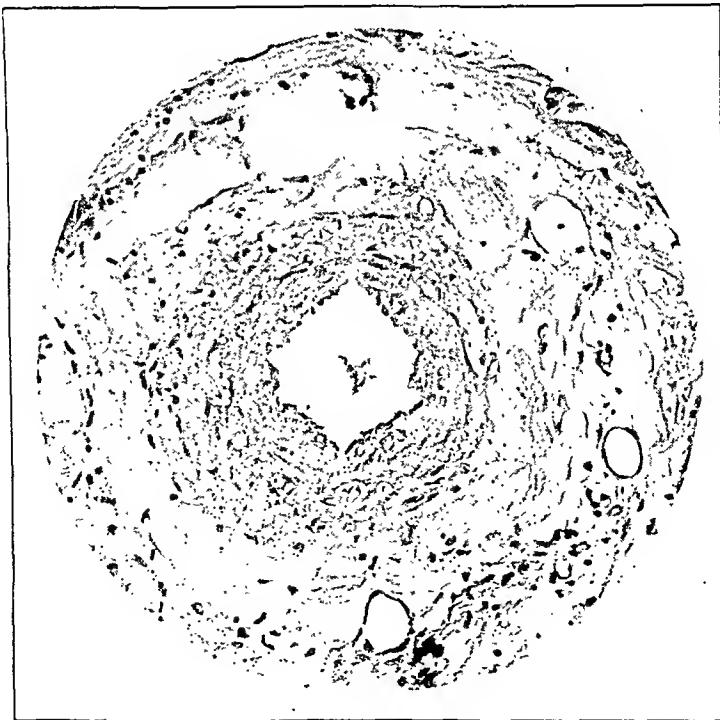


FIG. 6.—High-power photomicrograph of an artery, showing marked endarteritis and degeneration of the media and adventitia.

by the roentgenogram. Both lower lobes were dry, well aërated, and in small areas emphysematous, rupture of an air vesicle probably accounting for the pneumothorax. The bronchioles contained no mucus or other exudate. The right upper lobe was small, firm, poorly expanded, and densely adherent to the large mediastinal mass which formed the most conspicuous feature of the thoracic contents (Fig. 2). There was a small amount of bronchopneumonia in this region, extending outward from the medial surface of the lung for a distance of 1 to 2 cm. with an especially dense fibrous mass beneath the apical adhesions, an area suggesting organizing pneumonia. This entire upper lobe was somewhat atelectatic, while the middle and lower ones showed compensatory emphysema. The entire superior and middle, and part of the dorsal mediastina were completely filled with a solid tumor-like mass, about 6 cm. in thickness anteroposteriorly. It extended from the suprasternal notch to the pericardium and protruded anteriorly nearly to the sternum, presenting a hard, rounded convexity, at first suggesting an aneurysm, though very much more resistant. All the structures of the middle mediastinum were adherent or included within the mass, the aortic arch was displaced to the left of the median line and twisted into the anteroposterior plane. The aortic wall, however, was only loosely adherent to the mass, except at the root of the neck, where the left common carotid was also invaded and constricted. The right innominate artery was thus forced to take an oblique course across the root of the neck, and both it and the right carotid could scarcely be separated from the inflammatory tissue. The trachea was displaced to the left, as had been noted in the roentgenogram of the thorax. The left innominate artery was relatively unaffected. The left bronchus was infiltrated, especially over the inferior and anterior portions of its circumference. The right main bronchus, however, was much more seriously infiltrated and constricted, and was held rigidly fixed in the new tissue, while its lumen, not half a centimeter in diameter, could only be opened with difficulty with the point of the scissors.

The superior vena cava was surrounded and infiltrated throughout the whole of its course, more completely, however, posteriorly than elsewhere, as a solid mass of the growth intervened between it and the pericardium. The lumen of the artery was not completely obliterated, but admitted only a small probe, and the great induration and inelasticity of the mass seemed to prevent any expansion of the venous wall. The endothelium, however, remained smooth. The right internal jugular vein was constricted at its inferior end just above the point of its union with the subclavian. The left innominate vein was greatly encroached upon by the mass throughout the lower $2\frac{1}{2}$ cm. of its course, its lumen reduced to a mere slit, and, like the superior vena cava, nonexpansible, though not thrombosed.

The right vagus nerve was displaced forward and at the level of the subelavian artery entered the fibrous tumor, from which it could not be dissected. The recurrent laryngeal nerve on the right side was also so infiltrated that it could not be traced below this level, the fibrous tissue reaching to the trachea. On the left side the recurrent laryngeal remained free, and the left vagus nerve was relatively uninvolved. Fatty tissue representing the atrophied thymus gland and small lymph nodes in the ventral mediastinum were not involved, but numerous anthracotic bronchial nodes were completely surrounded by, and firmly embedded in, the inflammatory tissue.

Microscopical Pathology. Sections of the mass show an enormous mediastinal overgrowth of connective tissue far beyond any which we commonly see in fascial planes, and certainly beyond any reparative demands. The tissue is almost entirely fibrous, presents few nuclei, and has very limited blood supply (Fig. 3). Some of the foci of lymphocytes and other cells undoubtedly represent fragments of lymph nodes, but other areas are granulomatous (Fig. 4). The sections show uniformly a preponderance of broad hyaline connective tissue strands such as are seen in keloids, indeed one wonders whether the process is not to be regarded as of much the same type. It seems probable that infection caused an initial inflammatory reaction which, in healing, provided an extraordinary amount of connective tissue, and that hyalin degeneration supervened to the same extent as appears quite regularly in cutaneous scars in the negro race.

Nerves are compressed and infiltrated to the point of atrophy, and the vessel walls are constricted and their lumina much reduced. Groups of small newly formed vessels with intact endothelium and homogeneous, collagenous, outer walls are seen (Fig. 5). The walls of the older arteries are thickened by proliferation of the subendothelial fibrous tissue, and degeneration of the media has extended so far that it is difficult to recognize each coat (Fig. 6). The thoracic aorta shows an extraordinarily diffuse degeneration of the media, chiefly myxomatous. The other coats are little affected. Extensive perivascular infiltration is seen only in the adventitia of the aorta.

The apical lesion in the lung is of a chronic inflammatory type also. It is compressed, very poorly expanded, shows a diffuse growth of new fibrous tissue, many nodular collections of lymphocytes, and, very rarely, a giant cell. In some ways, therefore, there is a resemblance to tuberculosis, but endothelial cells and tubercles are extremely infrequent compared to the extent of the infiltration. It is possible that tuberculosis and syphilis may exist here together.

The peribronchial nodes which are included in the sclerotic tissue show almost complete obliteration of normal structure, only a portion of the peripheral sinus and a small amount of the lymphoid

tissue remaining. One giant cell, about which are scattered a few endothelial cells, was found in one of these portions of nodes. This lesion does not justify a diagnosis of tuberculosis, for the absence of caseation and the replacement of the rest of the node with the dense sclerotic material suggest rather a syphilitic granuloma. Other nodes are deeply anthracotic and show diffuse hyaline deposits along the course of the reticulum.

The cardiac muscle shows some atrophy throughout, but the only inflammatory change is a very slight round-cell infiltration underneath the endocardium.

The liver cells are slightly atrophic, due to chronic passive congestion, and small foci of round-cell infiltration in the perilobular tissue are present. This is of uneven distribution and represents an early stage in a cirrhotic process. Productive inflammation is not seen.

The spleen shows also a well-marked chronic passive congestion, but little or no fibrosis.

A Levaditi stain of these tissues failed to show spirochetæ.

Literature. The clearest description of this condition is to be found in a short paper by Lian, published in 1913. The author believed that a fibroid tuberculous mediastinitis attacks the inferior mediastinum, and that even the rapidly caseating forms with abscess formation, which may originate in the superior mediastinum, usually follow down the fascial planes and present inferiorly on the pericardial surface. Syphilis, on the other hand, is a disease of the superior mediastinum. A third diffuse form involving both is very rarely seen. In the syphilitic cases three types are described: the respiratory, which is characterized by inspiratory dyspnea, a whistling stertorous type of respiration, rapid, diminished breath sounds, substernal retraction, cyanosis without edema, and attacks of suffocation due to pressure on the recurrent nerves. In the superior vena cava type, which, it is generally agreed, is the most frequent one, the symptoms are almost entirely circulatory and respiration is difficult only on effort. Precordial pain, tachycardia, headache and epistaxis are seen, and cyanosis, which may be very intense or which may be present only when stooping over. The edema may be limited to the eyelids, conjunctivæ, parotid and supraclavicular regions.

Osler also gave considerable attention to the subject of superior vena cava thrombosis, collecting 29 cases. He differentiated between the clinical pictures produced by thromboses of each of the three great veins, describing the type of superficial venous dilatation characteristic of each. The venous dilatation of the superior type is chiefly vertical and appears in the eyelids and over the root of the neck and the first rib where prominent, parallel veins appear at right angles to the line of the rib. A connection is established with the perforating branches of the internal mammary veins. The anastomoses with the superficial epigastric veins take

place down the front of the thorax, and to a much less extent by way of the veins around the umbilicus and xiphoid. This may be differentiated from the picture in cases where the inferior vena cava is obstructed. A patient with this type of obstruction presents on the lateral chest walls enlarged thoraco-epigastric veins which enter the apex of the axillæ, anastomosing in the iliac regions with branches of the superficial epigastric veins. In portal obstruction the axillary trunks and parasternal branches are large, but the greatest dilatation is over the region of the diaphragm. Osler states that complete thrombosis of any one of these three veins may exist for years with reasonably good health and freedom from discomfort.

More lately Howard has taken a somewhat different view from that of the French writers regarding the etiology, believing that most of the cases are tuberculous, and only a small proportion syphilitic. He described in 1915 2 nonfatal cases, 1 of which had a long duration, seven years, with very marked dyspnea and cyanosis, hemoptysis and cough. Improvement occurred and was thought to be due to a regression and healing of the tuberculous process. Howard's second case is of the inferior mediastinal type, with adhesions, pericardial and pleural, due to empyema and possibly pericarditis.

The French writers, however, maintain the importance of syphilis as a factor, and Lian's paper is obviously the result of their observations.

The case of Comby is one of the few in which the clinical findings were substantiated by autopsy. In 1892 the patient was seen first with signs of obliteration of the superior vena cava and attacks of suffocation and retrosternal oppression. Syphilis had been present for six years and had been practically untreated. The symptoms were alarming; extreme congestion of the face, defective sight and hearing, headache, epistaxis and attacks of dyspnea with cyanosis. Under mercurial treatment the symptoms subsided, but coincident with this improvement there developed an anastomotic circulation which remained very obvious for seven years. The patient died in 1906 of general paralysis, and at autopsy the anterior mediastinum was filled with a mass of fibro-adipose tissue tightly adherent to the trachea, bronchi, and great vessels, especially the superior vena cava.

Sebillotte in a thesis published in 1912 analyzes 31 case records, but few are complete from the pathological standpoint. The author mentions syphilis as the chief agent and thinks that the original lesion may be a syphiloma of the trachea or of one of the bronchi. The terminal state of such a lesion is seen in such a specimen as was taken at autopsy from the case of Brander and Holroyd, but the early stages are rarely seen.

Renault in 1913 reviewed the subject and described a case which clearly belongs in this group clinically, though pathologically we

must reserve some doubt. The patient was a woman, aged thirty years. In 1909 she had pain in the anterior part of the thorax and sense of oppression. At times she suffered much pain and was cyanosed, with alternate aphonia and dysphonia. The symptoms were improved by medication with iodids, but in 1912 again appeared. Dyspnea became very severe and asthmatic attacks frequent, the thorax painful, dysphonia intermittent. The radiogram showed a heavy shadow in the mediastinum and the Wassermann test was positive. The symptoms again greatly improved under treatment with iodids, mercury and arsphenamine.

Others, as Blankenhorn, believe the obstructive respiratory types, which resemble the bronchial asthma cases, to be due to syphilis of the large vessels, usually the aorta, but occasionally the vena cava. Blankenhorn mentions, also, as most writers do not, the peculiarly varied character of the symptoms—the paroxysmal change in pulse rate and respiration, the sudden changes in lung volume, the laryngeal crises and bi-tonal voice or aphonia—a picture which is well shown in the writer's case.

We are indebted to Harris for the most complete survey yet made of mediastinal conditions as a whole, and while present methods of diagnosis would undoubtedly change some of his tabulations, they are, in general, no doubt very accurately made. Of the 185 cases which this author studied, he was able to find only a small group of chronic nonsuppurative inflammatory cases, and of these but one is of the type under consideration. It is described by him as "characteristic mediastinitis proper." There was "excessive fibroid induration of the upper pleuræ and lungs with matting in the upper mediastinum suggesting tumor, also apical tuberculosis with cavitation and extensive pleurisy. The pericardium was not affected."

Many cases characterized by progressively increasing dyspnea and cachexia, even when syphilis is known to be present, do not justify a diagnosis of mediastinitis, for in these a tumor or an aneurysm has been found at autopsy much more often than the fibrotic lesion of the fascia alone. Davis, however, reported with autopsy findings a lesion closely resembling the one under consideration, but with complete obliteration of the superior vena cava, due to an old thrombosis and periphlebitis.

Diagnosis. A study of the literature of the subject shows, therefore, that a diagnosis has most frequently been made solely upon clinical grounds—with perhaps a corroborative positive Wassermann reaction in the more recent cases—but often the therapeutic test has been the sole dependable basis for establishing a differential diagnosis. The older cases cited show that this has been given the weight of evidence most often, but we cannot overlook the fact that many cases of mediastinal pressure are yearly seen upon which an accurate diagnosis is never made. If the therapeutic test of mercury and iodids fails in a late stage of the disease, the

fact offers not even negative evidence, for a mass so avascular, so extensively fibrotic and hyaline and so unabsorbable, such as this tumor is, could not be expected to be influenced particularly by medication. Even careful clinical observation may leave a margin of doubt as to whether syphilis is the sole cause or merely coincident; whether it has damaged primarily the coronary vessels and so the myocardium, or whether the obstruction is just above the heart. Difficult to differentiate also may be a severe syphilitic degeneration with the peculiar type of cyanosis, dyspnea, and secondary polycythemia described by Ayerza and later by Warthin. It is also difficult to determine whether the aorta or one of its larger branches is the principal site of damage. Multiple small aneurysms have frequently been seen in the aortic arch, which if they happen to protrude in the antero-posterior plane without a noticeably widened arch, arouse little clinical interest. A thymus large enough to be of clinical importance is a great rarity after childhood, and it is rather the tumors of this gland which are entitled to serious consideration in adults. A substernal aberrant thyroid has been seen but not with sufficient frequency to permit of probable diagnosis. Enlarged tuberculous lymph nodes are of course by no means rare and in some cases, as in this and in Howard's, probably such a cause cannot be excluded. Hemoptysis has occurred in both diseases. The productive or granulomatous pneumonia of syphilis usually affects the lower lobes most prominently. The pneumothorax at first glance suggests tuberculosis, but with extreme dyspnea and emphysema it may occur in other diseases. Hodgkin's disease and lymphosarcoma are often primary in the mediastinal nodes, but so frequently do they involve the cervical or axillary chains that confirmatory evidence is usually obtained in this way and a diagnosis of these diseases is rarely considered conclusive at present unless it is made from examination of excised tissue. Other types of malignant disease, as the small cell or other widely infiltrating types of carcinomata from a latent tumor of stomach, bile ducts, or breast, may so closely simulate syphilitic mediastinitis as to require considerable time and observation to make a diagnosis. The trachea, bronchi and recurrent nerves may be to the same extent embedded in dense sclerotic tissue and respiration become equally difficult.

Of the 29 cases of superior vena cava obstruction collected by Osler, 7 were found to be due to syphilis, and only 1 to carcinoma. Another series might give a different proportion, but syphilis must be a relatively frequent cause.

It is well to remember that treatment to be effectual must be begun early before destructive or sclerotic processes have proceeded beyond the point of repair.

An asthmatic etiology may generally be determined or eliminated by careful observation of the symptoms. In our patient the early

appearance and persistence of dysphagia, the hemoptysis, the inspiratory type of dyspnea, all suggested at once some other cause than foreign protein sensitization. The latter principle, while offering new and fascinating explanations for many obscure conditions, should not divert us from anatomical lesions, and no consideration of monkey fur or the proximity of rodents divert us from thorough physical examinations and precise observations.

Conclusions. A case of chronic mediastinitis causing the death of a young colored woman is described.

Syphilis is believed to be the etiological factor.

The lesion is a dense hyaline connective tissue mass, with granulomatous areas, sclerosing and constricting bloodvessels, nerves and the large bronchi. The infiltration and productive inflammation closely simulate in extent and effect a malignant tumor.

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PRIMARY TUBERCULOUS PERICARDITIS, WITH REPORT OF A CASE.

BY WILLIAM B. RAWLS, M.D.,

NEW YORK.

ACCORDING to the literature, secondary tuberculous pericarditis is a fairly common disease but primary tuberculous pericarditis (in the pathologic as well as the clinical sense) is very rare. Hedblom, in a review of all the literature in 1921, found only 13 cases proved by necropsy. Because of this rarity, I believe it worth while to add another case report to the literature.

Case Report. (Hospital No. 164926.) A male negro, aged fifty-one years, was admitted to the hospital, May 27, 1924, complaining of (a) pain over the heart, (b) shortness of breath, (c) constant vomiting and (d) swelling of the feet. There was no history of tuberculosis in the family, and his past history was unimportant in reference to present illness. Syphilis was denied.

He was well and working every day until four months ago (January 20, 1924), when he began to tire easily and was short of breath on doing his customary work. At this time there was no swelling of the feet and no cough. The shortness of breath gradually increased, and three months later it was so severe that he was forced to quit work and go to bed. At this time he began to have dull aching pain over the heart, which was constant and did not radiate. He also noticed that on retiring at night his feet were swollen, but the swelling would disappear during the night. He now also began to have a dry and nonproductive cough. These symptoms persisted, gradually growing worse until he entered the hospital one month later. One week before entrance to the hospital he began to vomit. At first he vomited only two or three times daily, but vomiting became more frequent until date of admission, when he was vomiting almost constantly.

Physical examination revealed orthopnea, anxious expression and marked dyspnea, which was increased on the slightest exertion. The pupils were equal and reacted to light and accommodation. Deep reflexes were present and apparently normal. Lungs: There was evidence of consolidation over the lower left lobe posteriorly and congestion of the right lower and middle lobes posteriorly, as shown by the following physical signs: Expansion was poor and limited on the left. Tactile fremitus was increased over the lower right lobe posteriorly, but was absent over the lower left lobe posteriorly. There was dullness on percussion over the lower left lobe posteriorly and decreased resonance over the lower right lobe posteriorly. There was an absence of the breath sounds from the angle of the left scapula downward and suppression of breath sounds over the lower right lobe posteriorly. There were numerous small mucous rales over the right lung posteriorly up to the angle of the scapula and anteriorly to the fourth rib, and in the infra-scapula region on the left. Heart: There was no palpable thrill at the apex, and the apex beat was not felt. On percussion the area of cardiac dullness extended to the left to the posterior axillary line, downward to the sixth interspace and to the right 5 cm. from the midsternal line. On turning the patient from side to side there was a shifting in the area of cardiac dullness. The heart sounds were very weak and distant, and were barely heard with a stethoscope. No murmurs were present. The apex rate was 130 per minute, extrasystoles were present (20 out of every 130 beats), but there was no pulse deficit. Abdomen: The liver was enlarged

about 6 cm. below the costal margin in the midclavicular line and was tender on palpation; there was no evidence of ascites, but there was marked edema of the lower extremities. The urine showed a strong trace of albumin. The blood Wassermann test was negative. The patient was given digalen, 20 min., intravenously every six hours without apparent improvement. On May 29, thirty-six hours after admission, 600 cc of turbid hemorrhagic fluid, with a large amount of fibrin floating free in the fluid, was withdrawn from the pericardial sac by the substernal route. He was slightly improved following this aspiration, and on May 31 400 cc of the same type of fluid was again withdrawn, and the same amount of air injected into the pericardial cavity, but the patient died eight hours later. Culture on both specimens of fluid were negative after forty-eight hours' incubation. A guinea pig was injected with the pericardial fluid and necropsy on guinea pig six weeks later revealed miliary tubercles in the spleen, liver and lungs and an enlargement of the mesenteric lymph glands. A smear from macerated enlarged mesenteric lymph gland of the guinea pig showed tubercle bacilli present.

Necropsy: The following is an extract from the necropsy report: There was marked congestion of the lower lobe of the right lung. *The lymph nodes at the hilus of the lungs and of the thoracic cavity were not enlarged and showed no evidence of tuberculosis.* The lower lobe of the left lung was collapsed due to pressure from the heart. *On section of the lungs there were no calcified areas and no evidence of tuberculosis. The cervical and thoracic vertebræ showed no evidence of tuberculosis.* Heart: The pericardial sac occupied almost the entire left pleural cavity, extending 17 cm. to the left in the fifth interspace and 7 cm. to the right in the fourth interspace. On section of the pericardium it was seen to contain an abnormal amount of turbid hemorrhagic fluid. There was a marked proliferative pericarditis, both the fibrous and serous coats being much thickened and laminated, varying in places from $\frac{1}{4}$ to $\frac{3}{4}$ inch. The inner surface of the pericardium and epicardium was covered by a large amount of granulation tissue, to which adhered pedunculated masses of partially organized tissue. Some of these masses formed adhesions between the layers, imperfectly dividing the cavity into lesser cavities which contained turbid hemorrhagic fluid. The walls of the left ventricle were concentrically hypertrophied. The weight of the heart was 180 gm. The cavity of the left ventricle was small. The endocardium was smooth and glistening, and the valves were normal. The liver showed marked chronic passive congestion, with no evidence of tuberculosis. The spleen and kidneys were negative for tuberculosis. Mesenteric lymph glands were not enlarged and apparently normal. The mucosa of the intestine was smooth, with no evidence of ulceration; Peyer's glands apparently normal. The mucosa of the bladder was

normal; the prostate was enlarged, but on section showed no evidence of tuberculosis. There was no evidence of tuberculosis in any other part of the body.

Discussion and Summary. The above case was considered as one of primary tuberculous pericarditis; that is, it was proven to be tuberculous and clinically and pathologically it appeared to be primary, as no other focus of tuberculosis was found after careful search. The diagnosis was based on the chronicity, the presence of a relative large sterile effusion, guinea-pig injection and necropsy findings. Judging from the relative frequency at necropsy of pericarditis with adhesions of probable tuberculous origin in patients who have died of another disease, it is probable that a large proportion of patients with tuberculous pericarditis recover spontaneously. However, most patients with a large amount of effusion run a chronic course and die. The fluid reaccumulates; open drainage is followed by infection and the disease runs a characteristically downward course. In cases of secondary tuberculous pericarditis the course seems largely determined by the type and location of the primary lesion. In reference to the treatment, Weil, Wennekebach, Loiseleur and Oppenheimer have produced pneumopericardium with gratifying results, and concluded that the benefit derived is due directly to the effect of the air on the disease in a manner similar to the reputed effect of air on peritoneal tuberculosis. Postmortem statistics indicate that few disease processes are so frequently overlooked as those which effect the pericardium.

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LYMPHATIC LEUKEMIA IN INFANCY WITH THE REPORT OF A CASE.

BY MARTHA WOLLSTEIN, M.D.,

AND

FREDERICK H. BARTLETT, M.D.

(From the Babies' Hospital, New York.)

THE Babies' Hospital records show a total of 25,246 admissions. Fourteen instances of acute lymphatic leukemia and one of acute myelogenous leukemia are included in this number. Few patients over three years of age are admitted to the hospital. The age of the infants with lymphatic leukemia ranged between ten months and four years. The age of the only case of myelogenous leukemia was two and a half years.

The patient who furnishes the occasion for this report was a girl who died at fourteen months of age. The unusually interesting autopsy findings and the comparative rarity of lymphatic leukemia in infants of this age have led to a detailed report of the case.

Clinical Course of the Disease. G. F., aged twelve and a half months, was admitted to the hospital, March 17, 1924. The parents said she had been listless and pale for about three weeks, and breathing rapidly for two days before admission. There was no history of angina. Neither the family nor the birth history has any bearing on the case. She had always been well nourished. The present illness began with lessened activity and a gradually lessening desire to play. At the same time the mother noticed that the baby had been growing pale. The occasion for bringing her to the hospital was the sudden appearance of rapid breathing associated with extreme weakness, so that the child was in a condition resembling collapse when admitted.

Physical Examination. The baby looked acutely ill. The skin was bloodless, as were the mucous membranes. The breathing was rapid, regular and shallow.

Skin. There were scattered areas of bluish discoloration, but no definite petechial spots.

Abdomen. The abdomen was distended. The liver edge was felt 11.5 cm. below the costal margin and the spleen 9 cm. below. There was neither rigidity nor tenderness.

Mouth. The tonsils were moderately enlarged.

There were no other abnormal findings in any organs. The diagnosis made by the admitting physician was as follows: Acidosis; leukemia or aplastic anemia.

Course of the Disease in the Hospital. March 18. Because of the obvious anemia, confirmed by a blood count showing 824,000 red

cells per cu.mm. and 20 per cent hemoglobin, the child was transfused by the direct method with 190 cc of blood from the mother. Before transfusion the differential count showed 5 per cent polymorphonuclear neutrophils, 93 per cent lymphocytes, and 2 per cent basophiles. Six nucleated red cells were counted to 100 leukocytes. The blood platelets numbered 152,000 per cu.mm. The absolute number of mononuclear cells was 53,163, and of polymorphonuclears 3,997, while the normal numbers should have been 34,260 and 22,840 per cu.mm.

March 19. After the transfusion a few petechial spots were noticed over the posterior surface of both legs, more numerous on the right.

March 24. The child seemed much improved. There was no change in the size of the liver and spleen. Two pale blue areas were noticed on the skin over the back.

March 28. A small hemorrhagic vesicle appeared on the chin just below the lip. It was surrounded by ecchymoses, and the spot looked like a blueberry.

March 29. The child was given a transfusion of 160 cc of the mother's blood by the direct method.

April 3. The crust which had formed over the spot on the chin fell off, leaving a raw surface. A similar spot appeared on the left cheek. Another transfusion of 140 cc of the mother's blood was given by the direct method.

April 7. The baby took food well and was holding her weight, giving the impression of slight improvement.

April 8. Tryparsamide,¹ 0.35 gm., was injected intramuscularly into the buttock for its tonic or catalytic effect.

April 11. The general condition showed distinct improvement. The liver and spleen remained practically unchanged in size.

April 13. The patient was discharged because of her improvement, with instructions that she be carefully watched.

April 17. The child was brought for tryparsamide injection and blood examination. She showed a gain in weight from 7,270 to 7,580 gm. and a gain in the number of red cells and hemoglobin, both of which reached the high mark for the time of observation. This was fourteen days after her third transfusion.

April 25. She returned for treatment and again showed a gain in weight. However, the hemoglobin, the red cells and the leukocytes were all diminished and there were purpuric spots on the legs. Inguinal, axillary and epitrochlear lymph nodes were enlarged and the abdomen was distended. In the anterior axillary line the spleen reached 10 cm. below the costal margin and in the mid-axillary line the liver extended 10 cm. below. Readmission was advised because the child was evidently losing ground. Death occurred in the hospital on May 5.

Throughout the entire course of the disease, the urine had not shown anything abnormal.

The temperature was irregular in type. During the first two weeks in the hospital, it ranged between 100 and 103° F. After the first transfusion it reached 104° F. During the next two weeks it was lower, from 98 to 100° F., rising again to 101° and 102° F. during the week before she died and reaching 104.8° F. on the morning of her death.

Summary of Clinical Features. Marked pallor, rapid breathing with extreme weakness, fever, ecchymoses and petechial spots on the skin, enlargement of the liver and spleen, temporary improvement in the general condition following transfusions, then the rapid and progressive decline resulting in death mark the clinical course. The duration of the disease from the observation of the first symptoms to death was a week more than two months.

Discussion of Blood Findings. The red blood cells were lowest on admission (824,000 per cu.mm.). They rose after the first transfusion to 2,200,000, but fell back in eight days to 1,500,000. They rose again, after the second transfusion, to 2,224,000 and after the third transfusion increased steadily for two weeks to 3,184,000. After that the red cells declined in a week to 2,400,000 per cu.mm.

The hemoglobin ranged between 19 and 70 per cent, and the color index from 1.25 to 1, which is rather high. Vogel² found both high and low indices in his series of leukemia patients. Naegeli³ found the index regularly high in lymphatic leukemia.

The leukocyte count on admission was 57,000 per cu.mm. and on the next day it had fallen to 10,000. The count gradually dropped to 2050 on April 3. During this time, March 18 to April 3, the child received three transfusions. Nevertheless the leukocytes steadily dropped, which is important and significant as indicating that the transfusions had no apparent effect in stimulating the production of white blood cells.

The striking phenomena in the white count are: the total of 57,000 leukocytes on admission and the drop to 10,000 cells on the next day; the leukopenia, reaching a minimum of 2050, during most of her stay in the hospital; the terminal increase to 21,150 leukocytes on the day she died.

It is important to emphasize the point that acute lymphatic leukemia in infants may coexist with leukopenia, which leukopenia may be present during the greater part of the disease. In this instance, it lasted for one month, from March 24 to April 25. For a period of three weeks, tryparsamide was administered intramuscularly for its possible catalytic effect,⁴ in doses of 0.05 per kg. of body weight. Whether a sufficient amount of the drug had been given to affect the blood is open to question. It must be taken into consideration, however.

Necropsy Findings. G. F., aged fourteen months. May 5, 1924. An abdominal incision only was permitted. The body was that of an emaciated, white female infant. There were purpuric spots

on the skin of the face, chest, abdomen and lower extremities. The abdomen was distended. The superficial cervical lymph nodes, the inguinal and axillary nodes were symmetrically enlarged.

Liver. It weighed 875 gm. and extended 6 cm. below the lower border of the sternum and 7.5 cm. below the margin of the ribs in the mammary line. The transverse diameter measured 20 cm. and the right lobe measured 15 cm. anteroposteriorly. The capsule was smooth. On the surface and in the substance there were many round white areas, 1 to 2 mm. in diameter. These were surrounded by a narrow zone of congestion, giving a mottled red and yellow appearance (Fig. 1). On section the liver substance showed some fatty change and many leukemic nodules. In the transverse fissure

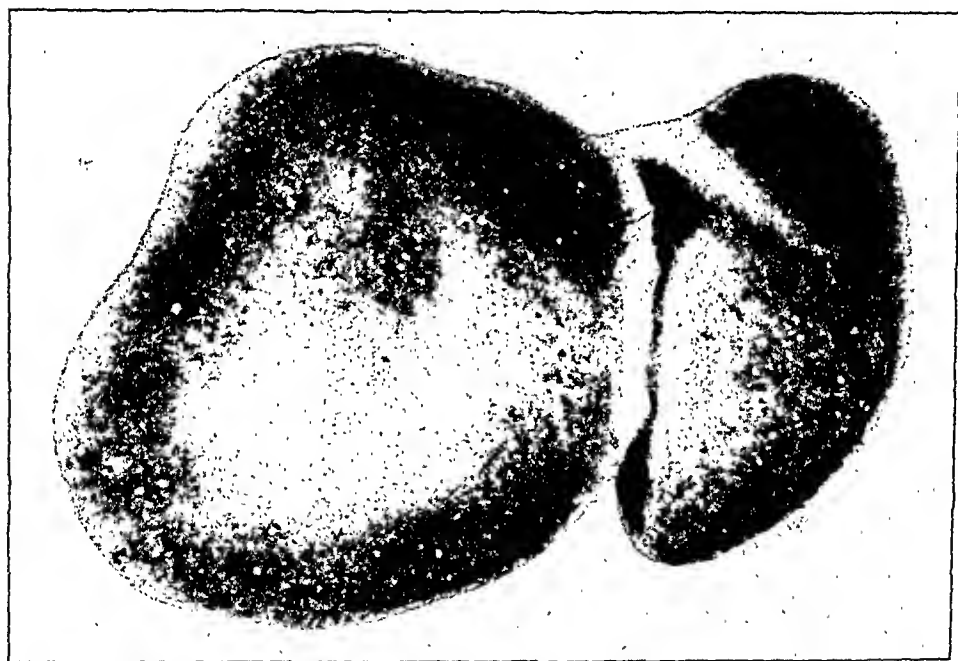


FIG. 1.—Liver showing leukemic nodules surrounded by zones of congestion.

there were several large lymph nodes. One of these measured 1 cm. in diameter and was hemorrhagic in its upper half, but pale in the lower portion.

The *spleen* extended to the upper border of the ilium, weighed 212 gm., and measured 12.5 by 8 cm. The capsule was smooth. There were a few subcapsular hemorrhages apparent (Fig. 2). The substance was rather soft. On section there were many small white nodules 1 to 2 mm. in diameter. In the hilus of the spleen there was a lymph node, 5 by 9 mm. in diameter.

The *stomach* was distended with food and also contained a small amount of blood-stained mucus. The mucosa showed many hemorrhages, some linear and some 1 to 2 mm. in diameter. There were no ulcers.

The *pancreas* was normal and firm in consistency. It showed many capillary hemorrhages beneath the capsule and into the substance. The lymph nodes along the upper border were markedly enlarged, dark red and 1.5 cm. long. On section they were fairly firm and had a smooth uniform appearance.

Intestines. The duodenum was normal. The jejunum showed visible solitary lymph nodes and small pinpoint hemorrhages in the mucosa. The Peyer's patches were not enlarged but they all showed small hemorrhagic areas. Just above the ileocecal valve



FIG. 2.—Spleen, greatly enlarged; deep red in color with subcapsular hemorrhages.

the follicles in a Peyer's patch were distinctly hyperplastic and red in color. In the large intestine, the solitary follicles were all slightly enlarged and hemorrhages into the mucosa were numerous. There were no ulcers in the intestinal tract.

The *kidneys* weighed 100 gm. and were large, pale, moist and firm. Leukemic nodules were present in the boundary zone and in the medulla. Several of the nodules were 3 mm. in diameter. Hemorrhages varied from 1 to 3 mm. in diameter. The markings were blurred.

The *suprarenals* weighed 3 gm. They were pale yellow and showed a narrow medulla.

Heart. The muscle was flabby. Subpericardial hemorrhages were present. On the surface of the aorta, there were a few small lymph nodes, the size of a pin head. The valves were quite normal. There were no leukemic nodules to be seen.

Lungs. There was no pleurisy. The left lung was emphysematous throughout the upper lobe, and the posterior portion of the lower lobe contained a hemorrhage 5 cm. in diameter, less in depth. The right lung was emphysematous in its anterior two-thirds.

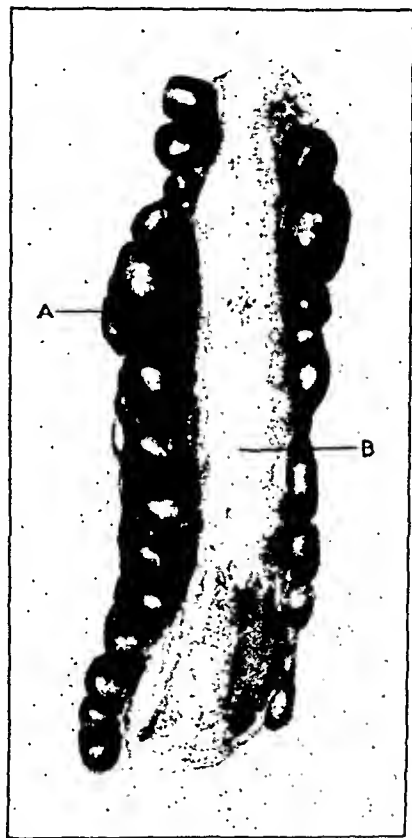


FIG. 3.—Chains of lateral lumbar lymph nodes, showing enlargement and hemorrhage, a; aorta, b.

Posteriorly the lower lobe contained a small atelectatic area, and the upper lobe an area of acute bronchopneumonia 2.5 by 2 cm. in diameter. Edema of both lungs was marked.

Lymph Nodes. The bronchial lymph nodes were all large and red in color. At the bifurcation of the trachea, the largest node measured 2.5 cm. transversely and 2 cm. vertically. On section small hemorrhages were apparent in the nodes. The substance was uniformly smooth, rather firm and very moist. A chain of lymph nodes along the aorta on both sides varied in size from 0.5 cm. to 1 cm. and in color from bright to deep red (Fig. 3).

All the abdominal lymph nodes were much enlarged, and pale red. The largest were just within the inguinal ring, where, on the right side, there was a dark red packet, 3.5 cm. in diameter, consisting of five nodes. Lying on the vertebral column was a chain of enlarged glands, many 1 cm. in length. On section, most of these glands contained hemorrhages.

Thymus. The gland was removed piecemeal and was apparently not enlarged. It was pale in color.

Bladder. The wall was very pale and contained many punctate hemorrhages into the mucosa.

Anatomical Diagnosis. Subcutaneous, subserous and submucous hemorrhages. Leukemic infiltration of liver and kidneys. Hyperplasia of spleen and lymph nodes (general). Acute bronchopneumonia. Pulmonary emphysema and edema.

Microscopic Examination. Liver. The liver lobules were small because collections of round, mononuclear cells occupied the interlobular areas and encroached upon the periphery of every lobule. The round cells were present within and without the intralobular and interlobular bloodvessels, which also contained red blood cells and a few larger mononuclear cells with vesicular nuclei. The Kupffer cells were distinct and in some places contained phagocytosed fragments. No fibrous connective tissue was seen. Such liver cells as remained were narrower than normal and many contained large drops of fat. The bile ducts and the bloodvessels lay surrounded by masses of small, mononuclear cells. As a consequence of the cellularly infiltrated periphery and the fatty central portion, no lobule in the section presented a normal appearance.

Spleen. The connective tissue septa were distinct and were not increased in size nor in number. Both small and large bloodvessels were filled with red cells. Small hemorrhages had occurred. Brown pigment was present in small amounts. A few Malpighian bodies could be made out with a normal central vessel, but the periphery shaded into the surrounding mass of mononuclear cells. Consequently the splenic pulp had the appearance of a mass of small, mononuclear cells with congested capillaries between them.

Lung. The vessels of the pleura were filled with blood cells. Intrapleural and subpleural hemorrhages were present. Some alveoli contained only red blood cells, while others contained only serum. The contents of other alveolar groups were polymorphonuclear leukocytes, which also infiltrated the alveolar walls. Fibrine was present in small amount in these alveoli. The lesion was one of edema, hemorrhage and early bronchopneumonia.

Bronchial Lymph Node. In the greater part of the node, the cortex and the medulla could not be distinguished because there was diffuse mononuclear cell packing of both. The connective tissue was normal in amount. Many lymph sinuses were packed with mononuclear cells, although some of the largest were almost

empty. No germ centers were present. Phagocytosis of pigment granules and nuclear fragments was going on by means of large cells within the sinuses. These large cells were very numerous and in some places contained an entire small cell besides pigment granules. The bloodvessel walls were quite normal.

Lymph Node No. 2. The lymph nodules at the periphery of the node and the strands in the center were outlined by areas of hemorrhage. The nodules themselves were closely packed with lymphoid cells. Hemorrhages had occurred into the periphery of neighboring follicles.

Heart Wall. The pericardium was normal. The bloodvessels between the muscle bundles contained many mononuclear cells, but there was no perivascular infiltration. The muscle cells were normal. There were no leukemic nodules in the section.

Aorta. The wall of the aorta and a cusp of the aortic valve were normal.

Suprarenal. The cells of the cortex had undergone granular degeneration and in some places especially in the glomerular zone, were lacking. The medulla was wide, congested and the seat of small hemorrhages. Within the bloodvessels were mononuclear cells.

Kidney. In the cortex there were many collections of mononuclear cells. These varied in size, and in some instances had replaced both tubules and glomeruli (Fig. 5). Practically every one of these cell groups contained one or more bloodvessels, small and normal in structure. The tubules of the cortex, both the convoluted and the arms of Henle's loops, showed marked peeling of their lining cells and contained granular material. The glomeruli were normal. There was no fibrous connective tissue increase. The collecting tubules were normal in size and in shape. Many of them contained granular or hyaline casts. In the wall of the kidney pelvis were many perivascular areas of mononuclear cells. The epithelial lining of the pelvic wall was normal. There were areas in the boundary zone where the mononuclear cell infiltration had become so diffuse that the appearance was that of adenoid tissue with straight tubules running through it.

Stomach. The lining epithelium and glands were normal. Between the glands there were collections of mononuclear cells. These were both larger and more numerous than is the case in the normal stomach. The other coats were edematous, but showed no cellular infiltration.

Microscopical Diagnosis. Acute lymphatic leukemia: leukemic infiltration of liver, fatty infiltration of liver; leukemic infiltration of spleen, kidneys, stomach mucosa, thoracic and abdominal lymph nodes; pulmonary edema; acute bronchopneumonia.

Discussion. The interest in this case centers about the diagnosis during life, in the light of the clinical symptoms, the course, the dura-

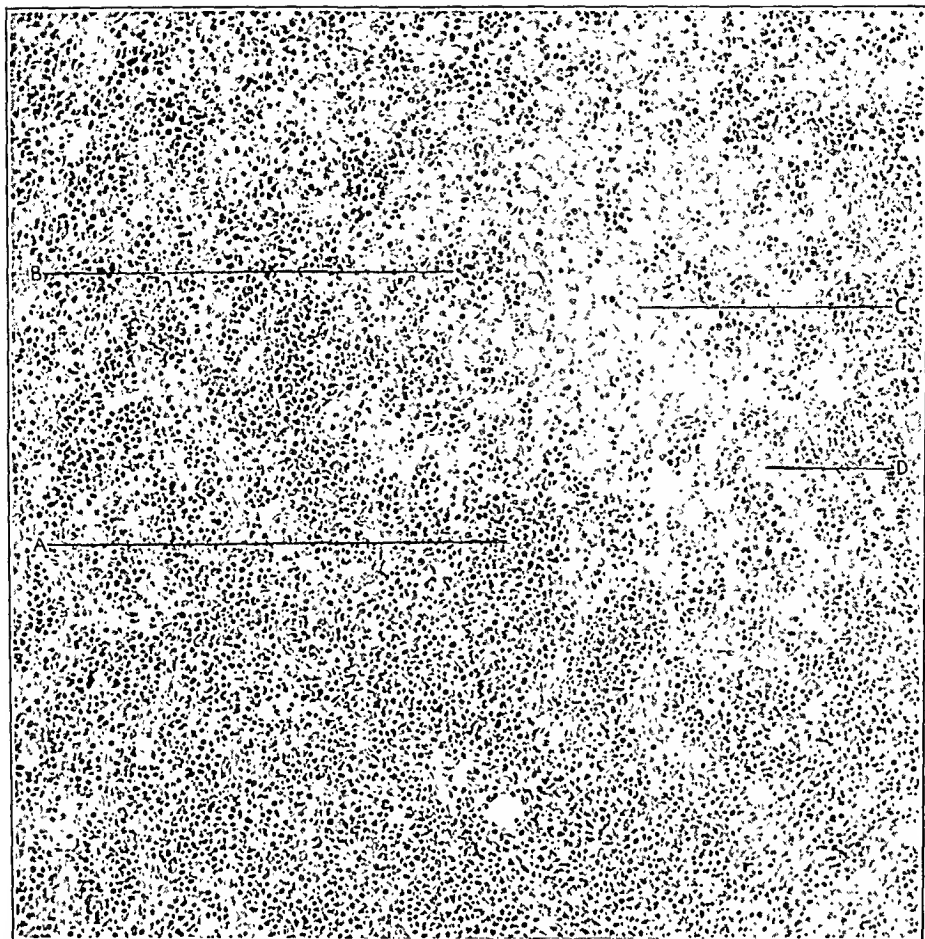


FIG. 4.—Liver, showing lymphocytic infiltration between (a) and within (b) the lobules; fatty liver cells (c); and normal liver cells (d).

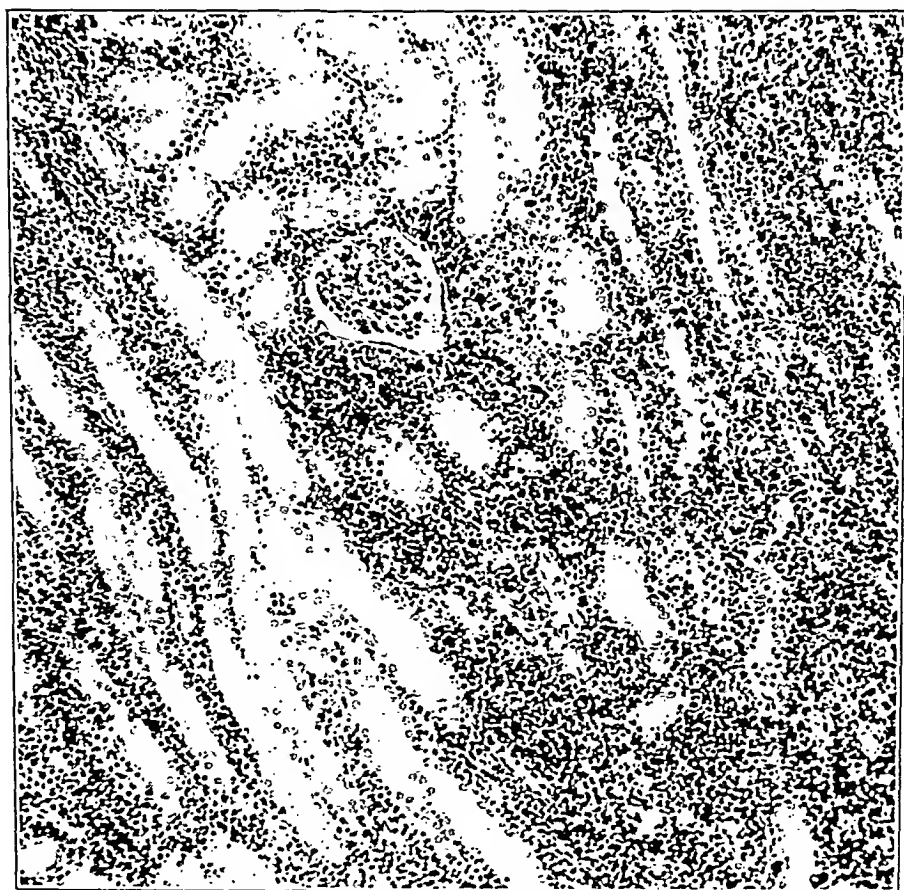


FIG. 5.—Kidney showing lymphocytic infiltration between the tubules and glomeruli.

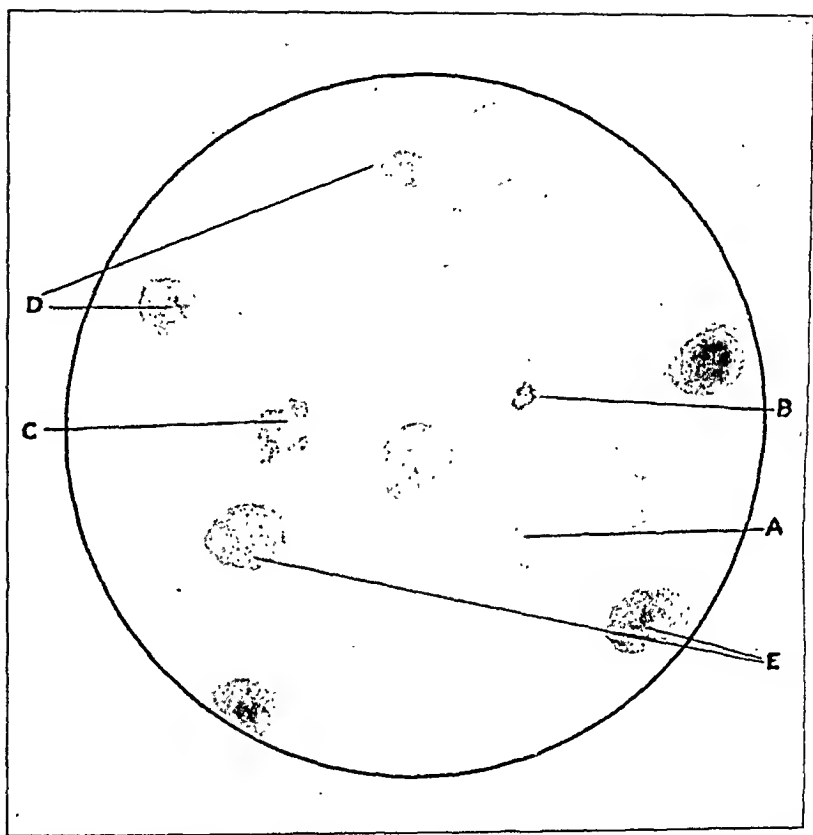


FIG. 6.—Smear of blood on March 18. *a*, red cell; *b*, normoblast; *c*, polymorphonuclear neutrophilic leukocyte; *d*, normal lymphocyte; *e*, pathologic lymphocyte.

tion and the blood picture. The postmortem diagnosis was apparent from the gross appearance of the liver, kidneys and lymph nodes, and was confirmed by microscopical sections of these organs.

The onset of the illness was characterized by gradually increasing pallor and listlessness over a period of three weeks, with sudden development of hyperpnea. This may have been due to diminished oxidation of the cells of the body. The cause of this, however, remains uncertain. The blood picture on admission suggested lymphatic leukemia because of the high number of leukocytes, the absolute preponderance of lymphocytes over granular cells and the reduction in the platelet count. Von Jaksch's anemia was excluded by the abnormally high number of lymphocytes, the comparatively few nucleated red cells and the absence of myelocytes from the blood, together with the absence of rickets, the presence of hemorrhages and the severity of the illness. The drop in the total number of leukocytes raised the question of whether we were dealing with an aleukemic stage of leukemia or with an aplastic anemia. The constant preponderance of the absolute number of lymphocytes over that of the polynuclear cells gave no aid, but the persistence of eight to ten nucleated red cells argued against aplasia. The hemorrhages from the mouth and the skin, and the rapidly downward course were in favor of leukemia. Aplastic anemia runs a much slower course and no case under one year of age has been recorded.

Transfusions were of only temporary help to red or white cells. That is, they either did not stimulate new blood formation, or they did not help to keep a normal number of cells in the peripheral blood.

The relative numbers of polymorphonuclear cells did increase after the first transfusion, and continued to do so for about one week, when a drop was apparent. After the second and third transfusions the polymorphonuclears increased again relatively, and more decidedly. Absolutely, however, the polymorphonuclear leukocytes never reached the number which is normal for the blood of a child of one year.

Among the cases of acute leukemia in infancy and childhood which have been reported, there are a number which show either an aleukemic stage or a completely aleukemic course. Baar⁵ described 3 cases of his own and quoted extensively from the literature. In Baar's first case, which he looks upon as one of mixed lymphatic and myelogenous leukemia, the leukocytes fell as low as 2,000 per cu.mm. In the case of Hess and Isaac,⁶ a boy aged three years, the leukocytes varied between 237,000 and 2000 in number. In our case the child came under observation with 57,000 leukocytes, which then rapidly fell to 2050 in spite of two transfusions. Before death the white cells had increased to 21,150. That the lymphocytes had been formed in much larger numbers than appeared in the

peripheral blood was shown by microscopical section of the kidney, liver and spleen. All these organs contained large collections of lymphocytes, evidently filtered out from the blood stream. Thus these cells in the circulating blood were decreased in number and the size of the viscera was increased.

The small mononuclear leukocyte which was the predominating cell in the blood from the first to the last day of the period of hospital observation, was round, with a nucleus which filled most of the cell body, contained a nucleolus and left a narrow cytoplasmic ring free from granules (Fig. 6.) The nucleus was often slightly indented. The resemblance to young myeloblasts was recognized, and the test for the oxidase reaction was made as a possible means of differentiation. The test proved to be uniformly negative, no granules being demonstrable in the cells under discussion, though the polymorphonuclear cells showed the dark blue granules characteristic of the reaction. The diagnosis of lymphatic rather than myelogenous leukemia then became certain, and was born out later by the microscopical examination of the organs. The absolute number of these mononuclear cells as compared with the polymorphonuclear elements was far in excess of the normal number for the child's age, and remained constantly so from first to last.

The platelets varied from 152,000 to 88,000 per cu.mm. being diminished throughout the period of observation.

We can see no point in designating a third variety of leukemia as due to "the large undifferentiated cell," as Wachi⁷ has done. Realizing that the oxidase reaction may be absent from some myeloblasts, as Naegeli³ has pointed out, we feel that only a tentative diagnosis can be made during life, and that the histology of the organs and marrow after death must be the final proof. Since, however, myelogenous leukemia is acknowledged to be exceedingly rare in infancy and even in early childhood, such a diagnosis will scarcely be accepted without postmortem confirmation, even should the oxidase reaction prove positive during life.

There are 14 cases on record at the hospital which were diagnosed as acute lymphatic leukemia on the blood findings, clinical symptoms, course and fatal outcome. Autopsies are lacking in all but two instances, chiefly because the patients died at home after being removed against advice. While we realize that if diagnosis of acute lymphatic leukemia in young children is to be unassailable, it must rest upon gross and microscopical study of the organs as well as upon clinical symptoms, there are nevertheless certain manifestations common to our 14 cases which will bear discussing.

There were only 2 girls, and 12 boys in the group. Minot and Isaacs⁸ state that while leukemia is three times as common in males as in females, in the first years of life girls are relatively more often attacked than are boys. Thus the youngest of Baar's cases, the only one under two years of age, was a girl. Gautier and Thevenod⁹

report the case of a girl one year old. They also collected 7 cases reported since 1909, of whom 4 were boys. The youngest case observed at the Babies' Hospital was a boy, ten months old. Smith's¹⁰ case occurred in a boy of six weeks.

It is noteworthy that rickets was absent from 11 of the 14 cases and that it was marked in only one child in the series. In no instance was a positive Wassermann reaction obtained. No child in the series recovered.

Hemorrhages were present in every case, and always into the skin, combined in some patients with bleeding from the mouth (gums or lips), nose, intestine, urinary tract or into the conjunctiva. Hemorrhage is an essential symptom of acute leukemia. In those cases in which platelets were counted, they were low in number.

The disease lasted from three weeks to five months. Morquio¹¹ says in this connection that in his cases the true leukemic phase was sometimes as short as a week, and that the preleukemic phase may last two to six months.

The red cells numbered from 500,000 to 3,000,000 in most of our cases. Only 4 patients had more than 3,000,000 red cells, and none had over 4,000,000 at any time during the course of the disease.

It is possible to group the cases according to the way the leukocytes varied. Thus, in 5 cases they decreased consistently, twice to a leukopenia (117,000 to 2500), three times remaining far above normal (123,000 to 55,000). In only 1 case did they consistently rise during the period of observation. Irregularities in the count occurred in 4 cases after transfusions and in 1 other after treatment with benzol. One case showed marked fluctuations in the number of leukocytes over a period of five months, with no therapeutic measure to explain the variations. The highest number recorded in this boy was 63,200 and the lowest 4500, the counts on successive days showing surprising differences. During an attack of otitis, the leukocytes remained in the neighborhood of 6000, but several months later, without any discoverable lesion, they rose from 15,000 to 60,000. Six cases showed an aleukemic stage of the blood during the period of observation, but only the one detailed in this paper ran an aleukemic course during the greater part of the duration of the leukemia.

The spleen was enlarged in every case in our series. In 5 children its lower border reached the iliac crest, while in 5 others it extended only 1 to 3 cm. below the costal border. In the other 4 it was 4 to 6 cm. below. The liver was enlarged to a moderate degree in 10 children, but in 4 others it reached the umbilicus.

The superficial lymph nodes were palpable in all these patients, usually noted as being the size of a small bean or shot. In one instance an axillary node was as large as a walnut. The nodes were always movable and discrete. In no instance were there any large deforming masses in the neck or elsewhere.

The onset was sudden in 7 cases, with fever and hemorrhage into the skin, accompanied by epistaxis in 4. The gradual onset in the other 7 children was marked by pallor, fatigue and anorexia accompanied once by abdominal pain and once (in the case of G. F.), by sudden development of hyperpnea.

In 2 cases which came to autopsy, the thymus was not enlarged. Rocaz¹² reported the case of a boy aged four years in whom acute lymphatic leukemia began with angina and proved fatal on the twenty-fifth day. The thymus gland weighed 200 gm.

Summary. A case of acute lymphatic leukemia in a female infant of fourteen months is recorded in clinical and anatomical detail.

An aleukemic phase of acute lymphatic leukemia in infants and young children is not uncommon. Consequently the diagnosis can only be made after repeated examination of the blood in conjunction with a study of the clinical symptoms and course.

Hemorrhage is an essential symptom of acute leukemia in infants, and the number of platelets is low throughout the disease.

Transfusions have only a temporary effect in raising the hemoglobin per cent, the number of the erythrocytes or the number of the leukocytes.

Macroscopical and microscopical leukemic nodules were found in the liver and kidney, while the spleen and lymph nodes showed diffuse infiltration with lymphocytes.

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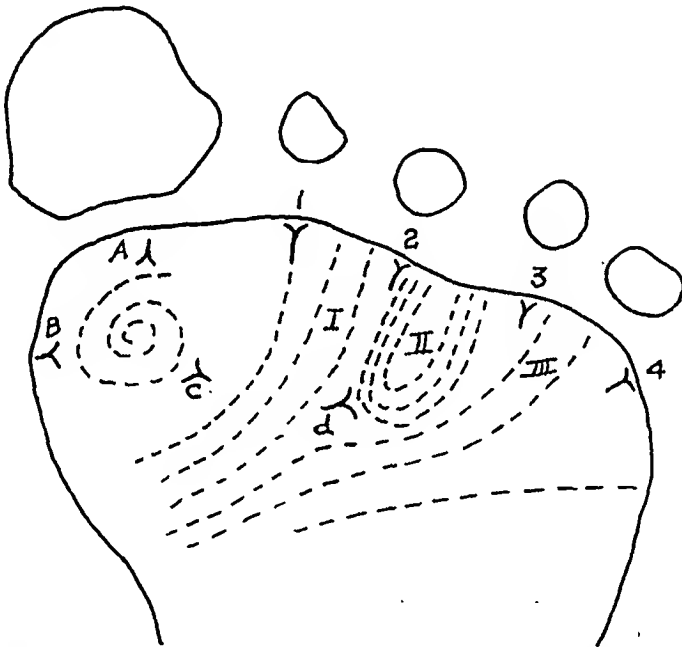
SOLE PRINTS OF NEWBORN BABIES.

By ROBERT B. MONTGOMERY, B.S., M.D.,

MADISON, WIS.

For a number of years certain hospitals, both lying-in and general, have been taking sole prints of the newborn babies, but to the best of my knowledge no effort has been made to read and classify the patterns found. In most cases two sets of prints are

taken—one to be given to the parents and one to be placed in the baby's (or mother's) chart. The prints are usually taken by the smeary, black-ink method commonly used in taking finger prints, and are of little value, either for correctly reading the details of the patterns or for correctly establishing the identity of the baby, should such an occasion arise. It rarely happens, to be sure, that a woman doubts the identity of the baby given her by the hospital attaches. If she should, how can it be proved without a shadow of a doubt that it is hers, and if not, whose it is? The method described is not intended to replace the usual methods of identifying the baby, but to supplement them, and is simple enough to be used by anyone after a little instruction.



Illustrating use of the formulæ. Hallucal pattern is a whorl (*W*). First plantar pattern is an open field (*O*); second is open at the top (*U*); third is an open field (*O*); giving combination 5 according to Wilder's table. Only one lower delta (*d*) is seen. Formula: *W5d*.

Prof. J. H. Mathews, of the University of Wisconsin, has perfected a process which is, to my mind, far superior to ink in making either finger, palm or sole prints. The details of the process have not yet been made public, but will be in the near future. Ink has proved very satisfactory in finger-print work where the papillary ridges are very large, but the ridges on the sole of a newborn baby's foot are so small and so delicate that the ink is pushed between them and only an unintelligible smear results. Naturally, the details of the patterns cannot be made out, and the method defeats the purpose. On the other hand, the method used by Professor Mathews gives a print which looks like a fine etching.

The details can be readily seen under a glass of about six diameters' magnification.

When the prints have been prepared the next step is to look for the patterns on the ball of the foot, and to reduce the description of them to a formula. Space does not permit a detailed description of the various patterns and lines, but some of the essentials will be explained. There are two general areas to be considered: The hallueal (area back of the great toe) and the plantar (area back of the other toes). There are five patterns in the hallueal area, the open field (no pattern), the whorl and the others (A, B, C) which denote which delta is missing. A delta is found where three papillary ridges come together to form a "Y." There are four digital deltas also, and between them lie the three plantar patterns. Below the plantar patterns are, at times, other deltas, from one to three. There are four general patterns in the plantar areas: O = open field; W = whorl; U = open at the top; Ω = open at the bottom. This gives in a general way the various patterns and deltas, and the reader is referred to articles by Wilder and Wentworth, and Cummins for more detailed descriptions.

Wilder and Cummins have proposed methods of formulation. They are both basically the same, but of the two I prefer Wilder's because it is simple. Wilder uses few descriptive suffixes, while Cummins uses so many prefixes and suffixes qualifying the primary symbols that his formulæ become too unwieldy for our purposes. A typical Wilder formula is W17dd, while one following Cummin's method is (A)U¹O¹⁴.O^{3111d}.U³.O¹⁴.2+3. To simplify matters, Wilder has proposed a table in which each plantar group is given a number: O O O = 1, O O U = 2, O O Ω = 3, etc. There are sixty-four combinations possible. The "d" denotes a lower delta. The plantar patterns are always read from left to right, and in making a formula for both feet the right is the numerator and the left the denominator of the fraction: $\frac{W6d}{A27dd}$.

In securing data on the probable occurrence of the various patterns and deltas, I took the prints of 191 newborn babies. The babies varied from one to seven days old and were taken in regular order as they were born at the Madison General Hospital. As some of the prints were impossible to read, due to errors in technic and otherwise, I secured only 163 double (both feet) prints; 342 single, of which 184 were male, 158 female, 172 right and 170 left. It is interesting to note that in a number of cases there was no trace of a pattern to be found, the whole field appearing only as a mass of dots. I feel that this is not due to an error in technic, but that the papillary ridges have not matured enough to produce definite lines. When this occurs it would be necessary to place the print in the undecipherable compartment.

Table I shows in detail the frequency of occurrence of the

different basic types of hallucal and plantar patterns, and of the various deltas. It is noticeable that the "A" and "W" patterns are the most frequent, while "C" occurs least often in the hallucal area. Only 19 whorls were found there which varied from the fundamental pattern.

TABLE I.—DETAILED TABLE SHOWING FREQUENCY OF OCCURRENCE OF VARIOUS PATTERNS AND DELTAS.

	Male.	Female.	Total.	Right.	Left.
Hallucal:					
A	87	79	166	87	79
B	22	19	41	23	18
C	3	3	6	4	2
O	5	8	13	6	7
W	58	39	97	47	50
tl	5	6	11	2	9
cp	2	0	2	0	2
lp	2	4	6	3	3
Delta:					
B	67	53	120	51	69
1	16	11	27	11	16
2	10	17	27	17	10
3	0	0	0	0	0
4	14	11	25	15	10
O	62	51	113	44	69
d	112	92	204	113	91
dd	10	15	25	15	10
ddd	0	0	0	0	0
Plantar:					
I O	150	123	273	133	140
U	11	10	21	13	8
Ω	23	25	48	26	22
W	0	0	0	0	0
II O	68	59	127	55	72
U	111	94	205	112	93
Ω	1	3	4	1	3
W	4	2	6	4	2
III O	162	143	305	150	155
U	19	14	33	20	13
Ω	2	1	3	1	2
W	1	0	1	1	0

No lower deltas were found in 113 cases, 1 in 204, 2 in 25 and in no instances were all 3 found.

In the first plantar area no whorls were found and the open field was the most common. In the second area the "U" pattern predominated. In the third area the open field predominated again, and in only 1 case was a whorl found.

Of the digital deltas, 79 were found on 342 prints, and in no case was the third seen. The reason for this conspicuous absence of most of the deltas is that it is very difficult to make contact between the skin under the toes and the paper. Here again is another instance why the Cummins method cannot be used in this

work, because much of the description of the plantar areas depends upon these deltas.

The sex of the subject and whether the print was taken from the right or left foot seems to have very little influence upon the frequency of occurrence of the various patterns and deltas (see Table I).

Table II gives in detail the number of times the various types of patterns occurred, and it agrees in the main with that found by Wilder. "A" formulæ were found 168 times; "B," 41; "C," 6; "O," 13; "W," 114.

TABLE II.—TABLE SHOWING FREQUENCY OF OCCURRENCE OF THE SINGLE FORMULÆ.

A1	58	B3d	1	W6dd	4
A2	1	B5	2	W7d	6
A2d	3	B5d	14	W9	1
A3	1	B6d	1	W9d	1
A5d	61	B6dd	2	W13d	1
A6d	5	B7d	2	W15d	1
A6dd	7	B21dd	1	W17d	2
A7d	5	B33d	1	W21d	2
A9d	1	B37d	2	W21dd	5
A13d	1	B41d	1	W23dd	1
A17d	5	C1	1	W33	1
A20d	1	C5d	1	W33d	2
A21d	2	C6d	1	W37d	4
A21dd	5	C21dd	1	W45d	2
A23d	1	C37	2	W(tl)1	2
A29dd	1	O1	4	W(tl)5d	7
A33	1	O5	4	W(tl)7d	2
A33d	2	O5d	2	W(cp)5d	1
A33dd	1	O6d	2	W(cp)37d	1
A37d	5	O6dd	1	W(lp)5d	4
A41d	1	W1	21	W(lp)7d	1
B1	13	W2d	2	W(lp)37d	1
B3	1	W5d	39		

Next comes the problem of filing the prints. When they are taken it is advisable to give one set to the parents and to keep one for the hospital records in order that they may be used for comparison in the future, if necessary. For filing, it is suggested that a 5 by 8 inch card be used. At the top space is provided for recording the name and address of the parents, date, case number and the formulæ of the patterns. In the large space remaining the prints can be pasted (trimmed a bit if necessary). In this way not much space is used, and as both of the prints are pasted on a card there is less danger of one or both being lost. These cards are not to be placed with the baby's chart, but in a separate filing cabinet. The question of how many drawers it would be necessary to buy must be determined by the number of births occurring at the hospital. If there are only a few (150 to 200) a year, only a few drawers will be needed to start; but if there are several hundred during the year it would be advisable to purchase the whole twenty-five.

To come to the actual filing of the records. The hallucal patterns determine the drawer the card is to go into. The first drawer is labeled $\frac{A}{A}$, the second $\frac{A}{B}$ and so on. The complete list of combinations is:

A	A	A	A	A	B	B	B	B	B	C	C	C	C	C	O	O	O	O	O	W	W	W	W	W
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
A	B	C	O	W	A	B	C	O	W	A	B	C	O	W	A	B	C	O	W	A	B	C	O	W

Of course it is possible to put two or three of these primary classes into one drawer because patterns occur rarely in some of them (see Table III).

The secondary classification is found by referring to the number denoting the plantar patterns. There are 64 of these groups, and as there are two feet to be considered, right and left, it makes 4096 possibilities, or secondary subdivisions. These need to be made only from time to time, as new formulæ occur. The tertiary subdivision is determined by the lower deltas, and the order is:

o	o	o	o	d	d	d	d
—	—	—	—	—	—	—	—
o	d	dd	ddd	o	d	dd	ddd

, etc.

Some of the compartments will soon be overcrowded, as $\frac{A1}{A1}$, and a simple method for further subdivision will have to be worked out. It has been suggested by Wilder that a ridge count be taken from the center of the hallucal pattern to delta B, but as delta B was found only 120 times in 288 cases, excluding B and O, it is impractical. It must be remembered that taking sole prints of a baby and of an adult are not the same thing by any means. The adult will hold his foot still, and will roll it to the medial side on request so that delta B will print, but a newborn baby will do no such thing, and if there is anything that can wiggle more than a little baby, I have yet to see it. This disinclination on the part of the baby to remain quiet is the chief reason why finger prints are not taken. As an aid to further subdivision of the more common patterns, I would suggest that the pattern on the ball of the great toe be incorporated in the general formula in some manner.

Let us suppose, for instance, that Mrs. A. says that the baby given her when she leaves the hospital is not her own, but another. How can we prove that it is her child? When the baby was born two sets of sole prints were made. One was given to the parents and one placed in the files. New prints are taken of the disputed child and compared with the two original sets, and if they are the same there can be no question as to its identity. But if they do not how can we determine who the child is? The formula of the disputed child is, let us say, $\frac{A1}{W5d}$. We would turn to that compart-

TABLE III.—SHOWING FREQUENCY OF OCCURRENCE OF COMPLETE FORMULÆ.

A1		A33		A13d		C5d		W2d	
A1	17	A3	1	W7d	1	B1	1	W21dd	1
A1		A33d		A33d		C21dd		W5d	
	2		1		1		1		3
A5d		A7d		W1		C6d		W1	
A2d		A37d		B1		C37		W5d	
	1		2		1		1		14
A17d		A5d		A5d		O1		W5d	
A5d		A37d		B1		O5		W5d	
	9		1		4		1		4
A1		A6dd		B1		A5d		W7d	
A5d		A37d		B5d		O1		W5d	
	14		1		1		1		1
A5d		A21dd		B3		B5d		W13d	
A5d		A38dd		B5d		O1		W5d	
	1		1		2		1		1
A7d		A7d		B5d		O6d		W15d	
A6d		A41d		B5d		O5d		W6dd	
	1		1		2		1		1
A1		A6d		B7d		O6d		W5d	
A6d		A5d		B5d		W1		W6dd	
	1		2		1		3		1
A21dd		B1		B21dd		A1		W21dd	
A6dd		A17d		B33d		W5d		W7d	
	1		1		1		1		1
A7d		O5		B3d		A1		W5d	
A6dd		A37d		B37d		W5d		W21dd	
	1		1		1		1		1
A27dd		O5d		B5d		A5d		W6dd	
A17d		A1		B37d		W6dd		W33d	
	1		3		1		1		1
A2		W1		B6dd		A21dd		W9d	
A17d		A2d		B5		W21d		W37d	
	1		1		1		1		1
A2d		W17d		O1		A7d		W1	
A20d		A5d		B6d		W33d		W37d	
	1		3		1		1		1
A5d		W1		O5		A9		W21d	
A21d		A5d		B5d		W39d		W37d	
	1		2		3		1		1
A5d		W5d		W5d		A1		W23dd	
A21dd		A5d		B5d		W1		W37d	
	1		1		1		4		1
A6d		W37d		W7d		W1		W33	
A23d		A6d		B6d		W1		W45d	
	1		2		1		1		1
A5d		W5d		W5d		W5d		W7d	
A29dd		A6dd		C37		W2d		W45d	
	1		2		1		1		1
A1		W21dd		A6d		W17d		W9	
A33									
	1								
A1									
A		B		C		O		W	
— 64		— 1		— 1		— 1		— 9	
A		A		A		A		A	
A		B		C		O		W	
— 2		— 13		— 1		— 1		— 41	
B		B		B		B		W	
A		B		C		O			
— 2		— 2		— 1		— 2			
O		O		C		O			
A		B		C					
— 16		— 5		— 1					
W		W		O					

ment in the file and by comparison the child could be identified. The number of different combinations possible with the simple method of formulation described above is more than one would expect at first glance. There are 25 hallucal combinations, 4096 plantar and 16 by the lower deltas. These figures multiplied together give 1,638,400 possibilities. Further subdivisions would give almost innumerable combinations.

The question of identity of a newborn baby rarely arises in a well-regulated hospital, but when it does it seriously affects all concerned. If a complete sole-print file has been carefully kept the matter can be settled easily in a very short time, and, perhaps, an expensive law suit averted.

It has been proved beyond all doubt that the papillary ridges on the balls of the fingers do not change their patterns throughout life, and it is only reasonable to suppose that those on the sole of the foot do not. However, it remains for some investigator to settle this point definitely.

Summary. 1. The new method of taking finger, palm and sole prints as devised by Prof. J. H. Mathews is far superior to the old ink method.

2. The method of formulation of the plantar patterns as worked out by Wilder is simple and practical.

3. The necessity of absolutely identifying the newborn babies is apparent to anyone giving a little thought to the matter, and is best done by sole prints.

4. Not only will prints prove valuable during the first few weeks of life, but in later years, when questions of identity often arise. It has been noticed many times that after death by fire or accident, when the body has been mutilated beyond recognition, that the soles of the feet remain intact, having been protected by the shoes. Identification would be a simple matter if sole prints of the individual were available. It would be a splendid thing for the country if it were required to file sole prints along with the birth certificate.

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THE INFLUENCE OF THE GALL BLADDER ON INTESTINAL MOTILITY.

BY BENJAMIN M. BERNSTEIN M.D.,

BROOKLYN, N. Y.

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THE question of gall-bladder function as well the diagnosis and treatment of its diseased conditions have held a prominent part on the stage of medical research in the last few years. Despite considerable work we are still in the dark on many fundamental facts concerning this interesting organ. We have been taught that its function is that of a reservoir and medium for concentrating the bile during its stay there. The gall-bladder bile is darker and of greater consistency than the liver bile; it has a greater percentage of bile salts and cholesterol; it contains mucin, a nucleo-albumin, not found in the liver bile. If the gall bladder is purely a reservoir, why was it placed on a side path, instead of in a direct line as in the kidney-ureter-bladder-urethra system? Furthermore, why is a reservoir supplied with glands and deep duets lined with glandular epithelium, if the latter have no secreting function? the mucous membranes, which secrete mucus only, have no glands. These and other questions in gall-bladder function still await solution at the hands of modern scientific research.

In the field of diagnosis, both the roentgenologist and the internist have tried their skill with but questionable success. George, L. G. Cole, Leonard, and others, have written much on the "direct" and "indirect" evidence of gall-bladder disease on the roentgen-ray film. The percentage of cases in which positive roentgen-ray shadows of the gall bladder and its contents can be shown and the diagnostic value of such visualization, are questions of doubtful significance. As a matter of fact, both L. G. Cole and Leonard have agreed that the "indirect" signs are of much greater value than the "direct" method (by indirect signs, we refer to the changes produced by the gall-bladder disease on surrounding organs).

Latterly, Graham, W. H. Cole, and Coppler of St. Louis, have brought out another method, that of visualizing the gall bladder and its contents by filling it with an opaque contrast solution. For this purpose they have used the calcium salt of tetrabromphenolphthalein which is excreted by way of the bile and thus finds its way into the gall bladder after intravenous injection. The method is not without discomfort and even danger to the patient, is difficult of operation, and extremely problematical in its diagnostic value.

When one studies the autopsy records of the large medical centers in this and other lands, he finds that the occurrence of gall stones

in man is a rather frequent one. Statistics seem to show that 10 to 12 per cent of all people coming to autopsy have gall-bladder calculi, with and without symptoms. Such being the case, one doubts the diagnostic value of mere visualization of the gall bladder and its contents, regardless of how perfect in this respect any method may become. One is inclined to divide his cases into "calculus carriers" and "calculus patients."

The secondary effects of gall-bladder affection, however, do offer valuable data by which our diagnostic ability may be bettered. It also gives us clues, which if properly studied and evaluated, will help us to clear up some of the questions regarding gall-bladder function. It is a well-known fact that gall-bladder disease is the most frequent cause for the production of reflex gastrointestinal symptoms. During the course of routine roentgen-ray examination of patients with gastrointestinal symptoms, we always made a six-hour observation after the ingestion of a barium and buttermilk mixture. We found a number of cases with an unusual type of intestinal motility, and learned that these patients had been referred to us as cases of cholecystitis or cholelithiasis; some of these were operated upon subsequently and pathological states of the gall bladder were found.

To describe intestinal motility of the barium meal, we must divide the opaque column as having a "head, a body and a tail." Depending on where the various parts of the column are found at the six-hour period, we classify the type of motility as normal, hypermotility and hypomotility. In these cases we observed a type heretofore undescribed, which we have chosen to call "strung-out," in other words, we found that although the "head" of the column was seen in the distal half of the colon, the "tail" was still in the jejunum with the "body" "strung-out" between the two points. Barring diffuse peritonitis with extensive adhesions, this type of motility was never observed in any other gastrointestinal disease or affection. Of course we did see a number of cases of gall-bladder disease without this "strung-out" motility; but whenever we saw this disturbance, we found we were dealing with a gall-bladder affection.

Through the kindness of Professor Wenckebach and the coöperation of his roentgenologist, Dr. Hitzenberger, the writer was enabled to perform a series of experiments on dogs in an attempt to discover the cause of this rather peculiar phenomenon. The dogs were fed with a meal consisting of barium and yoghurt, in addition to the various other substances used in our investigations, observations being made six hours after the ingestion of the meal. We first determined the normal intestinal motility of 5 dogs on repeated examination. Then 4 of the dogs were operated upon and complete cholecystectomy performed; the skin was permitted to heal before observations were again made. When these animals were then examined, we found that each one of the 4, now showed a "strung-out"

motility on repeated search. It was natural to assume that here was the cause of our unusual motility disturbance; that it was the absence of the gall-bladder function which was the factor, whatever that function may actually prove to be. Drawing conclusions a bit further, we were able to say that whenever we saw this motility irregularity in a patient with gastrointestinal symptoms, we were dealing with an absence of gall-bladder function, due to closure of the cystic duct, regardless of what the cause of such closure may be; and that those cases of gall-bladder disease which did not show this change, had no obstruction of the cystic duct.

How were we to explain our observations in the light of our present knowledge? We found an observation by Rohde that 72 per cent of patients who had cystic duct closure, showed a hypoacidity, which persisted in 90 per cent of them, years after cholecystectomy had been performed. Hohlweg believes the achylia found by him in cases of cystic duct closure, to be due to the absence of gall-bladder function, be that what it may. The following experiments were then performed in order to discover, if possible, what there might be in the gall-bladder bile which made it different from the liver bile, the absence of which substance created this disturbance in intestinal motility.

Experimental Work. **EXPERIMENT 1.** The 4 cholecystectomized dogs and 1 normal dog were given 5 cc each, of gall-bladder bile with their barium meal. After six hours, we found that the animals operated upon had their motility restored to normal, and that the normal dog showed an increase in his usual motility. It is rather interesting to note at this point, that Dastre in 1891 observed that feeding dogs with gall-bladder bile produced in them a diarrhea.

EXPERIMENT 2. Sodium taurocholate and glycocholate (0.4 gm. each) were added to the meals of the 5 dogs. There was no change in motility, either in the normal or in the cholecystectomized animals.

EXPERIMENT 3. An alcoholic extract of gall-bladder mucosa was made and given to the dogs with their meals, without change in motility.

EXPERIMENT 4. The dogs were fed with an aqueous extract of gall-bladder mucosa added to their meals, without influencing the motility either in the normal or in the operated animals.

EXPERIMENT 5. Two other extracts were prepared: One, after an aqueous and an alcoholic extract had been taken from the mucosa; another, from the fresh gall-bladder mucosa. Both of these extracts, when given to the dogs with the barium meal, showed a restoration to normal motility in the operated dogs and an increase in motility in the normal dog.

EXPERIMENT 6. Cholesterin (0.3 gm.) with the meal showed a restoration to normal motility in the cholecystectomized dogs, and no effect in the normal dog.

EXPERIMENT 7. Cholesterin (0.3 gm.) plus ether extract of mucosa added to the meal produced no change in the dogs operated upon, and showed some increase in motility in the normal.

Each one of the above experiments was performed at least twice and therefore the element of chance can be definitely ruled out.

Now let us make a resume of our observations before we draw conclusions. We find that the feeding of gall-bladder bile produces a restoration of the disturbed motility to normal, in the cholecystectomized animals, and an increase in motility in a normal dog. Furthermore, the bile salts given in fairly large doses are ineffective; the same applies to the aqueous and alcoholic extracts of gall-bladder mucosa. Cholesterin produces a restoration to normal motility in the operated dogs, and has no effect on the motility of the normal animal. Finally, an ether extract of gall-bladder mucosa restores the disturbed motility in the cholecystectomized dogs and an increase of motility in the normal dog; also, whereas cholesterin alone does restore the motility in the experimental dogs and has no effect in the normal, when given with the ether extract of gall-bladder mucosa, it produces then no effect in the cholecystectomized dogs, though the combination does increase the motility of the normal animal.

What are the conclusions which can be drawn from these interesting observations? First, that the gall bladder is not merely an organ of concentration and a reservoir for the excess bile. After its removal, there is a definite disturbance in intestinal motility. Further, the feeding of whole gall-bladder bile, causes a restoration of the disturbed motility to normal. Then again, large doses of bile salts which may be concentrated in the bladder produce no change in the irregular motility. Finally, cholesterin, a substance likewise concentrated in the bladder, does affect the disturbed motility in the cholecystectomized animals, though it has no effect in the normal dog; however it loses its efficacy as such when combined with an ether extract of gall-bladder mucosa, given to the dogs without their gall bladders.

Second, the gall bladder has a definite secretion, the product of its glandular activity, which has a stimulative, perhaps a regulatory influence on intestinal motility. An ether extract of gall-bladder mucosa, prepared even after an aqueous and an alcoholic extract has been taken, produces a definite restoration of the disturbed motility caused by cholecystectomy. Moreover this extract seems to have an inhibitory effect on the apparent stimulative effect of cholesterin in intestinal motility in the cholecystectomized animals. Furthermore, whereas cholesterin had no effect in the normal dog that had his gall-bladder function intact, this ether extract did affect the motility when given with the cholesterin, demonstrating its strength even in the normal.

Conclusions. We believe that: (1) This substance secreted from the gall bladder is of hormonal type, an activator; (2) that it has a regulatory effect on intestinal motility, and (3) that its absence produces an imbalance in the normal correlated action of the circular and longitudinal muscle fibers of the intestinal tract.

We venture to suggest, merely as a theoretic possibility, that the permanent or even temporary absence of this substance in the gall bladder, may be the exciting cause for the production of the primary cholesterin calculus, in permitting a precipitation of the cholesterin in the bile, where it may be held in solution by the presence of this substance.

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EXPERIMENTAL STUDIES ON THE COLOR OF THE BILE FROM THE GALL BLADDER AND LIVER.

BY A. WINKELSTEIN, M.D.,

AND

P. W. ASCHNER, M.D., F.A.C.S.,

NEW YORK.

(From the Surgical Laboratories of the College of Physicians and Surgeons, Columbia University, New York.)

THE introduction and wide clinical application of the Meltzer-Lyon method of studying the biliary tract has given rise to controversy concerning important points in the physiology of the gall bladder. Experimental studies upon the pressure factors in the duct system of the dog¹ and upon the entrance of bile into the duodenum² have been reported by us. These studies were undertaken in an effort to clarify the mechanism of the entrance into and the exit of bile from the gall bladder.

The origin and significance of the dark "B" bile is of prime importance in the application of the Meltzer-Lyon test. Lyon

and those who follow his teachings maintain that dark bile comes from the gall bladder. Others, notably Einhorn,³ maintain that this is not invariably the case, and that dark bile may be recovered in patients who have had a cholecystectomy performed. We have attempted, therefore, to study this question experimentally in the dog by intubating separately the common duct, one hepatic duct and the duodenum, with the gall bladder *in situ*, and with the gall bladder excised.

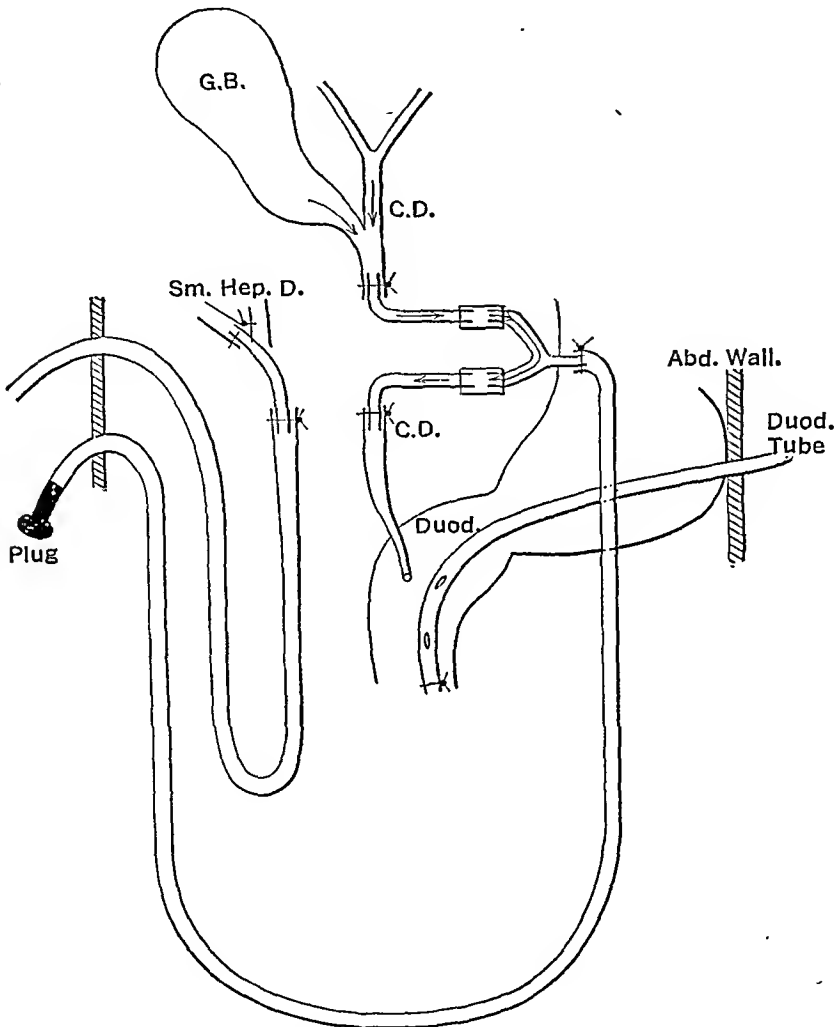


FIG. 1.—Diagram: G. B., gall bladder; Duod., duodenum; C. D., common duct; Sm. Hep. D., small hepatic duct.

Method of Study. We are indebted to Drs. Rous and McMaster,⁴ of the Rockefeller Institute for their method of avoiding infection by the use of long intra-abdominal rubber tubes.

By using a system of cannulas and connecting tubes, bile was permitted to enter the duodenum in a relatively normal manner, but could be sampled at will from the ducts and the duodenum (Fig. 1). A small glass cannula was introduced into the common

duet toward the liver and tied in securely at a point below the entrance of the cystic duet. A second cannula was introduced into the common duet toward the papilla of Vater at a point lower down, and similarly secured. The duet was completely severed between them. By short pieces of tubing the cannulas were connected with the branches of a small glass Y tube, and the latter secured by a suture through the round ligament. From its long arm a tube was led down into the pelvis and then upward and out through a small stab wound under the right costal margin, a bent glass cannula preventing occlusion at the turning point. By keeping this outlet tube plugged, except when aspirating it for purposes of securing a sample, the bile from the liver and gall bladder was permitted to pass through the branches of the Y tube into the lower segment of the common duet through the papilla into the duodenum. That bile did pass into the intestine was proved by the fact that the animals had well-colored stools throughout the observations made upon them.

To obtain pure liver bile for comparison a small cannula was inserted and secured in the small hepatic duet which, as described by Rous and McMaster,⁵ enters the common duet at a distance below the cystic duet. The cannula was at times inserted into this very small hepatic duet through the segment of common duet which it entered and which was situated between the two cannulas previously inserted in the common duet. The cannula was likewise connected with a rubber tube leading down to the pelvis and then upward and out through another small stab wound in the right lateral abdominal wall. The bile from this tube was permitted to drain constantly into a small sterile test tube. According to a technique described in previous experiments,⁶ a soft tube was passed through the anterior wall of the stomach, and guided into the duodenum. The free end of this tube was brought out through a small stab wound under the left costal margin. This permitted aspiration of duodenal contents, instillation of magnesium sulphate solution, etc.

The operations were performed under ether anesthesia through a median incision. As all tubes were brought out through lateral stab-wounds the primary incision could be closed completely. The procedure took from one to one and a half hours, depending upon the technical difficulties of introducing the cannulas into the duets, and securing them in proper position.

Experiments. EXPERIMENT 1.—Dog No. 3920. Male, weighing 12 kilos. Ether anesthesia. Median laparotomy. The procedures above detailed were carried out. The observations are recorded in Table I. The animal died on the fifth day of general peritonitis, due to rupture of a small abscess around the gastric fistula. The tubes and cannulas were found in good order.

TABLE I.—GALL BLADDER IN SITU.

Time, postoperative.	Conditions.	Color and Character of the Bile or Fluid.		
		Common Duct aspiration.	Hepatic Duct drainage.	Duodenum aspiration.
20 hours	Fasting	5 cc; dark green-brown	3 cc; light brown	7 cc; lighter brown.
21 "	Fasting; 40 cc MgSO ₄ in duodenum	8 cc; similar, dark	1½ cc; light yellow	Yellow.
25 "	Fasting	2½ cc; dark, tarry	Light brown	Light brown.
44 "	Fasting (drank water)	8 cc; dark, tarry	4 cc; yellow bile	Yellow.
45 "	Fasting; 40 cc MgSO ₄ (as above); observation for 1 hour	3 cc; very dark brown	1 cc; yellow	Pale yellow.
3 days	Fasting	3 cc; very dark brown	9 cc; yellow (collected over 24 hours)	Yellow.
3 "	Fasting; 40 cc MgSO ₄ (as above)	2 cc; very dark brown	Yellow	Yellow.
3 "	Ate sugar and eggs	4 cc; very dark brown	Yellow	Yellow.
4 "	4 hours after eating broth, bread, meat	5 cc; greenish-brown	Yellow	Yellow.
4 "	5 hours after food, 40 cc MgSO ₄ (as above)	Yellow-brown	Yellow	Yellow

Comment. Although this animal lived only five days, the observations seem of value. With the single exception of an observation made five hours after food, the common duct tube contained dark, tarry or greenish-brown, bile (mixed gall bladder and liver bile). The duodenal contents at the same time, however, varied from light yellow to medium brown, hence not accurately mirroring the appearance of the bile in the common duct. The isolated hepatic duct drained a light yellow bile throughout, either after fast, after food, or after instillation of magnesium sulphate.

TABLE II.—GALL BLADDER IN SITU.

Time, postoperative.	Conditions.	Color and Character of the Bile or Fluid.		
		Common Duct aspiration.	Hepatic Duct drainage.	Duodenum aspiration.
15 minutes	Under anesthesia	Dark, green-brown	Light yellow-brown	Brown.
19 hours	Fasting	3 cc; dark green-brown	1 cc; lemon-yellow	Turbid brown.
24 "	Drank water only; 40 cc MgSO ₄ injected in duodenum	2 cc; dark green-brown	½ cc; lemon-yellow	Watery brown.
48 "	Dog died; cause of death not found at the autopsy.			

EXPERIMENT 2.—Dog. No. 3923. Male, weighing 13 kilos. The procedure was the same as in the previous experiment. This animal died forty-eight hours after operation, and although the observations are therefore of limited value they are recorded in Table II. The cause of death was not ascertained at autopsy.

EXPERIMENT 3.—Dog No. 3924. Female, weighing 12 kilos. In this animal the upper cannula was inserted into the common duet at a point below the entrance of the posterior hepatic duet. All the bile was therefore sidetracked through the Y tube (Fig. 2).

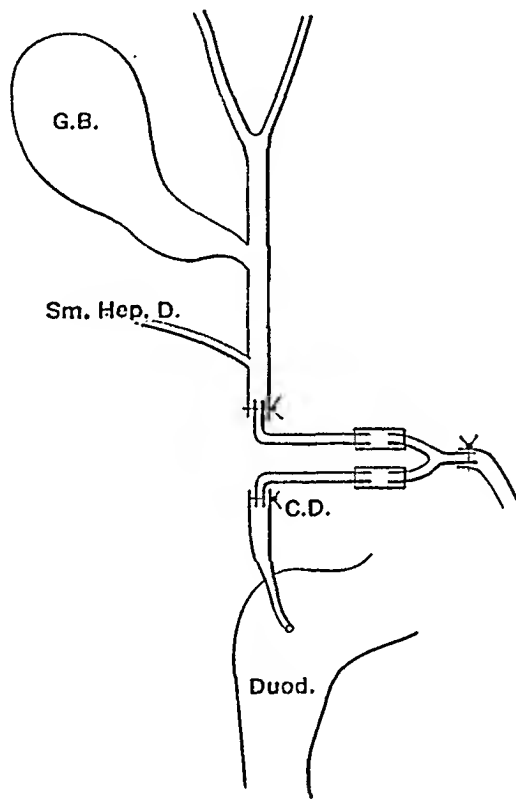


FIG. 2.—Diagram: Common duct shunted below entrance of the small hepatic duct.

Cholecystectomy was performed. The duodenal tube was inserted as in the preceding experiments. At autopsy, on the thirteenth day, the tubes were well walled off by adhesions. The duets were not dilated. The cystic stump showed no evidence of regeneration.

Comment. In this experiment, in which cholecystectomy was performed, the bile in the common duct and the duodenum was observed during the fasting state, after food and after the injection of magnesium and sodium sulphate into the duodenum. Throughout the entire experiment, after the first twenty-four hours, the bile in the common duct, although varying in the rate of flow, was constantly a light yellow color and quite thin. Even after a

prolonged fast of forty-eight hours, and after a markedly increased flow following the eating of meat, the color did not become darker. It was also noticed that the duodenal contents did not correspond very closely to the common duct contents, varying from a pale opalescent to a lemon-yellow to a muddy brown fluid.

TABLE III.—GALL BLADDER EXCISED.

Time, postoperative.	Conditions.	Color and Character of the Bile or Fluid.	
		Common Duct aspiration.	Duodenum aspiration.
24 hours . .	Fasting	1½ cc; dark green-brown	Lighter brown.
25 " . .	Fasting; 40 cc MgSO ₄ in duodenum	1½ cc; dark green-brown	Brown.
32 " . .	15 hours after, meat and water	2 cc; yellow-brown	Lighter brown.
33 " . .	15 hours after, meat and water; 40 cc MgSO ₄ in duodenum	½ cc; lighter yellow-brown	Yellow fluid.
3 days . .	15 minutes after meat, bread and broth	3 cc; golden-yellow	3 cc; lighter yellow.
4 " . .	Fasting 24 hours	3 cc; golden-yellow	Lighter yellow.
4 " . .	Fasting 24 hours; 40 cc MgSO ₄	2½ cc; lighter yellow	Yellow-tinged.
4 " . .	15 minutes after, food	3 cc; golden-yellow	Turbid, faint yellow.
5 " . .	Fasting 26 hours	2 cc; golden-yellow	Dirty brown.
5 " . .	Fasting 26 hours; 40 cc MgSO ₄	½ cc; golden-yellow	Lemon-yellow.
5 " . .	Eating 100 gm. meat	In 10 minutes, 5 cc; gold- en-yellow	Lemon-yellow.
6 " . .	Fasting 24 hours	1½ cc; golden-yellow	Lemon-yellow.
7 " . .	Fasting 18 hours	2 cc; golden-yellow	Lemon-yellow.
7 " . .	Fasting 18 hours; 25 cc Na ₂ SO ₄	1 cc; lighter golden	Lemon-yellow.
7 " . .	Bread and water	2½ cc; lighter yellow	Lemon-yellow.
8 " . .	Fasting 24 hours	2 cc; golden-yellow	Muddy brown.
8 " . .	Fasting 24 hours; 40 cc MgSO ₄	1 cc; golden-yellow	Lemon-yellow.
8 " . .	Ate 100 gm. meat	In 3 minutes 5 cc; golden- yellow	Lemon-yellow.
9 " . .	Fasting 24 hours	2½ cc; golden-yellow	Lemon-yellow.
9 " . .	Fasting 24 hours; 40 cc MgSO ₄	In 20 minutes 2½ cc; golden-yellow	Pale fluid.
9 " . .	Ate 150 cc meat and broth	In 20 minutes 5 cc; golden-yellow	Pale fluid.
11 " . .	Fasting 48 hours	3½ cc; golden-yellow	Pale yellow.
12 " . .	Fasting 18 hours	2½ cc golden-yellow	Pale yellow.

EXPERIMENT 4.—Dog. No. 3928. Male, weighing 10 kilos. Two cannulas were placed in the common duct and connected up as in the preceding experiment. The duodenum was not intubated at this time. Aspiration of the tube fifteen minutes after the operation revealed the presence of dark green-brown bile in the common duct. During the next eight days the bile was aspirated daily

fifteen to eighteen hours after food, and on each occasion 8 to 12 cc of dark green-brown to tarry, viscid bile was obtained. On the eighth day, under ether anesthesia, the abdomen was opened and a cholecystectomy was performed. The gall bladder was normal, and contained 5 cc of dark bile. The ducts were not dilated. The dog recovered perfectly from the operation, and observations were made on the appearance of the bile in the common duct for nine weeks. These are given in Table IV.

TABLE IV.—AFTER CHOLECYSTECTOMY.

Time after Cholecystectomy.	Conditions.	Character of the Bile. Common Duct aspiration.
24 hours	Fasting 60 hours	3 cc; medium brown.
2 days	4 hours after food	3½ cc; golden-yellow.
3 "	Fasting 24 hours	3 cc; golden-yellow.
3 "	Immediately after food	1½ cc; golden-yellow.
4 "	Immediately after food	2½ cc; golden-yellow.
7 "	Fasting 60 hours	2½ cc; slightly darker.
7 "	Immediately after eating meat	1 cc; golden-yellow.
8 "	Fasting 24 hours	2½ cc; golden-yellow.
9th to 16th day	Fasting 24 hours	2½ cc; golden-yellow (each day).
9th to 16th day	Immediately after food	1½ cc; golden-yellow (each day).
17th to 20th day	Fasting 72 hours	2 cc; medium brown bile.
During the next 26 days	Fasting 18 to 24 hours	2½ cc; golden-yellow (each day).
During the same 26 days	Immediately after food	2 cc; golden-yellow (each day).

Nine weeks after the cholecystectomy, under ether anesthesia, a duodenal fistula was made opposite the papilla of Vater and a soft tube sewed in it at this site.

Observations. Twenty-four hours postoperative: Dog fasting; 2½ cc of yellow bile in the common duct, and the duodenal contents were light yellow; 40 cc of 25 per cent magnesium sulphate solution was injected through the fistula into the duodenum. During the next hour there was no change in the color of the bile in the common duct or in the duodenum. Forty-eight hours postoperative: Fifteen hours after food similar observations were made. Seventy-two hours postoperative: Dog fasting twenty-four hours; both in the fasting animal and after magnesium sulphate the bile still remained unchanged in color. Four days after operation the dog died.

Autopsy. The cause of death was not found. The common duct above the upper cannula was widely dilated, measuring 2 cm. in width and 3 cm. in length, and contained light yellow bile. The short portion of the common duct below the second cannula

was also somewhat dilated. The liver tissue appeared normal with no widening of the intrahepatic ducts. Extrahepatic dilatation of the biliary duct system follows cholecystectomy almost regularly in experimental animals.⁷

Comment. This experiment provided the exceptional opportunity for studying the bile from the common duct with the gall bladder in, and after its removal, and later when influenced through a duodenal fistula. It is apparent that in a fasting animal with its gall bladder *in situ* the bile in the common duct varies from a dark greenish-brown to a brown-black in color and is quite viscid. After cholecystectomy in the same animal, however, with the exception of the first twenty-four hours after the operation and after a three-day fast at which times it may be medium brown. the bile is invariably and uniformly lemon to golden-yellow in color and is quite thin. The injection of magnesium sulphate in the duodenum of the cholecystectomized dog did not change the color of the bile in the common duct.

Discussion. The experimental results indicate that the gall bladder is the source and cause of the dark bile. Apparently the bile coming directly from the liver, although containing a varying amount of bilirubin, is always yellow. The bile, however, from the gall bladder and liver (in the common duct) of the fasting animal is quite dark, ranging from a tarry or deep greenish-brown to a dark brown. That the gall bladder is responsible for this change in appearance is proved by the fact that after cholecystectomy the same animal, fasting, feeding or influenced by magnesium sulphate in the duodenum, exhibits only yellow bile in the common duct.

To what extent these experiments are applicable to clinical physiology, especially the Meltzer-Lyon test, may not be conclusively stated from our experiments. In the Meltzer-Lyon test the sequence of bile colors is observed in the duodenal contents, while in these experiments the observations are concerned chiefly with the types of bile found in the biliary ducts. It may be said, with reference to our observations of the duodenal contents, that their color imitates somewhat but not closely, the appearance of the bile in the common duct. Probably local dilution and chemical factors change the appearance of the duct bile.* Nevertheless, it seems highly probable that the dark color of the duodenal specimen which is obtained clinically in the normal individual by the Meltzer-Lyon method is caused by the gall bladder. Inasmuch as our experiments deal only with normal animals, nothing can be said of the appearance of the bile in certain pathological states, either local or general, which may modify the color of the bile.

Summary. By means of cannulas placed in the biliary ducts and connected as described above, it was possible to observe the appear-

* In a number of these and previous experiments the intestine of dogs in which the indwelling duodenal tube was carried for a number of days showed erosions of the mucous membrane in the vicinity of the end of the tube.

ance of bile from the dog's liver alone (through one hepatic duet) and from the gall bladder and liver together (through the common duct). By means of a gastroduodenal tube, the contents of the duodenum could likewise be observed. These fluids could be sampled separately and simultaneously without diverting the bile from the intestinal tract to any great extent. The observations were made in animals with the gall bladder *in situ* and after its excision. With the exception of a possible change in the rate of filling and emptying of the gall bladder, due to the artificial elongation of the common duct system, relatively normal conditions were maintained.

1. Bile in the common duct of fasting dogs under the experimental conditions was dark greenish-brown in color and almost tarry in consistency, when the gall bladder was *in situ*.

2. Bile obtained directly from the liver, that is, from a hepatic duct, was a light yellow color whether the dog was feeding or fasting. Exceptionally it was of a medium brown color in the first twenty-four hours after operation.

3. After cholecystectomy the bile from the common duct was light yellow and thin in consistency whether the dog was feeding or fasting.

4. The instillation of 25 per cent magnesium sulphate solution into the duodenum was not followed by any change in the color of the bile from the common duct either before or after cholecystectomy, under these experimental conditions.

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AN ESTIMATION OF THE CLINICAL VALUE OF THE VAN DEN BERGH TEST.*

BY ELIZABETH GLENN RAVDIN, M.D.,

HENRIETTA HECKSHER MEMORIAL FELLOW, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA.

(From the William Pepper Laboratory of Clinical Medicine and the Medical Division
of the University of Pennsylvania.)

THE work discussed in this paper is the result of the application of the van den Bergh test for bilirubin in the blood serum in 140

* Read before the Pathological Society of Philadelphia.

cases in which there appeared to be an indication for such a test. It was undertaken with a view to determining the clinical accuracy and value of the test.

The methods previously in use for determining the presence of bile pigment in the serum were of two types—one depending upon the oxidation of bilirubin to biliverdin and the other upon the comparison of the color of the serum with a standard which approximated the color of normal serum. The first type of test, of which the Gmelin test is an example, depends upon the development of the green color of oxidized bilirubin when concentrated nitric acid is added to the serum. A concentration of bilirubin high enough to give a positive reaction is also high enough to produce discoloration of the tissues; so as a method of determining small amounts of bilirubin in the serum this group of tests is of no value. In the second type, as in the Meulengracht¹ test, the color of the serum is compared to a standard color, a dilute solution of potassium bichromate for example, which is so prepared that it matches the color of the average normal serum. The serum must then be diluted to match the standard, the amount of dilution being measured. The possibilities of error in this method are several. In the first place the test is not specific for bilirubin. Though they occur but rarely, other pigments may discolor the serum, such as carotin, biliverdin and perhaps urobilin. Also, slight hemolysis, which not uncommonly occurs after the blood is collected, will make it impossible to compare the serum with the standard. The most important source of error is due to the wide variation in the color of normal sera, so that slight variations due to increased bilirubin content will fall within the necessarily wide limits of the normal readings.

Van den Bergh,² in his search for a method by which small variations in the bilirubin content of the serum could be detected, recalled the diazo reaction which Ehrlich³ had described in 1883. The reaction depends upon the development of an azo dye, azo-bilirubin, when an acid solution of a diazonium salt is added to an alcoholic solution of bilirubin. Pröscher,⁴ in 1900, identified and isolated this dye, but no clinical use of the reaction was made until the work of van den Bergh and Schnapper⁵ in 1913. These latter experimenters found that pure bilirubin in a dilution of 0.7 mg. per liter gave a positive reaction to this test, and that biliverdin and other substances in the blood serum did not react to it. This then opened the way for the study of inaugural stages in diseases in which variations in the concentration of bile pigment in the blood occur.

While using the diazo reaction for quantitative determinations of the bilirubin in serum, van den Bergh noticed that in certain cases of jaundice it was unnecessary to bring the bilirubin into an alcoholic solution to obtain the azo dye, but that merely the addi-

tion of the diazo reagent produced the reaction. It was evident that bilirubin might be present in the serum in different forms. He then found that in the cases in which a tumor or stone caused obstruction of the common duct the addition of alcohol was unnecessary, and that this was also true of normal diluted bile. In the cases in which bilirubinemia was associated with a blood disease the addition of alcohol was necessary to produce an immediate reaction. Also in hemorrhagic effusions into serous cavities when the presence of bilirubin was determined quantitatively an alcoholic solution was necessary to produce the prompt diazo reaction. From these observations he drew conclusions which led to a new conception of jaundice. While it is true that this conception is based almost entirely on theory, it is at present the best interpretation of the different reactions obtained in the various types of jaundice.

The two types of jaundice which van den Bergh differentiated between are to be understood as two general groups, depending upon the location and type of the pathological lesion. For an understanding of this classification a brief summary of the theories of pigment formation must be given.

The reticuloendothelial cells, found most abundantly in the liver, but also in the spleen and lymph glands as well as in other portions of the body, are, according to the work of Kupffer,⁶ Aschoff,⁷ McNee⁸ and others, concerned with the breaking-down of the erythrocytes and the formation of bilirubin from the liberated hemoglobin. The bilirubin which is thus formed is then presumably present in some form in the blood stream. From the blood it is absorbed by, or passes through, the polygonal cells which line the biliary capillaries and is excreted by way of the bile. The bilirubin found in small amounts in the serum of normal persons and in greater amounts, due to increased hemolysis, in such conditions as ietero-anemia reacts differently from the bilirubin in an obstructive jaundice. The latter, as stated previously, reacts in the same manner as the bilirubin found in the bile. To the jaundice of obstruction van den Bergh gave the name "mechanical jaundice," while the jaundice of hemolysis or of liver disease he calls "dynamic jaundice". He assumes that the reason for the difference in reaction of the two is due to some action which the polygonal cells may have on the bilirubin, and therefore any pigment which has passed through these cells is of the obstructive type.

Method. Five cubic centimeters of blood is drawn from the vein into a dry test tube and allowed to clot. The serum is then removed by a pipette.

The Qualitative Test or Direct Reaction. To 1 cc of serum is added 1 cc of freshly prepared Ehrlich's diazo reagent. The time of the appearance of the maximum color is noted. If a reddish-

violet color develops within the first thirty seconds the direct reaction is said to be immediate. If no color appears until after thirty seconds, but does appear later, and it may not appear for as long as an hour, the reaction is delayed direct. If no color appears it is a negative reaction. If some color appears before thirty seconds, but grows more intense after that time, it is a mixed reaction, immediate and delayed, or biphasic direct.

The diazo reagent, which must be made immediately before the test is made, is a mixture of two solutions, each of which will keep for a month at least.

<i>Solution A.</i>		
Sulphanilic acid		1 gm.
Concentrated HCl		15 cc
Distilled water	q. s.	1000 "

<i>Solution B.</i>		
Sodium nitrite		0.5 gm.
Distilled water		100 cc.

To 25 cc of Solution A add 0.75 cc of Solution B.

The Quantitative Test or Indirect Reaction. To 1 cc of serum add 2 cc of 96 per cent ethyl alcohol and centrifuge. To 1 cc of the supernatant fluid add 0.25 cc of Ehrlich's diazo reagent and 0.5 cc of 96 per cent ethyl alcohol.

The result will vary from a faint pink color, as in normal serum, to a deep violet, depending on the amount of bilirubin present. The color is read in a colorimeter, such as the Hellige, against a standard, made up as follows:

STANDARD.

<i>Solution I.</i>		
Ammonium ferric alum		0.1508 gm.
Concentrated HCl		50 cc.
Water	q. s.	100 "

This is a stable solution, keeping indefinitely. It is 1 to 320 normal.

<i>Solution II.</i>		
Solution I		10 cc.
Concentrated HCl		25 "
Water	q. s.	250 "

This solution will keep one month. It is 1 to 8000 normal. The standard is made up of:

Solution II		3 cc.
10 per cent ammonium sulphocyanate (or 20 per cent potassium sulphocyanate)		3 "
Ether		12 "
Shake thoroughly.		

The ether extracts the color from the solution and forms a supernatant layer which is transferred to the colorimeter as the known

standard. In cases in which the concentration of bilirubin is too high to be read against the standard in the colorimeter, the standard may be concentrated by adding only half the quantity of ether. In order to avoid error from evaporation of the ether standard, transference of the solution to the colorimeter should be rapid and the readings made at once.

The standard matches in color a dilution of 5 mg. per liter of bilirubin. This dilution is the standard unit in terms of which the concentration of bilirubin is stated. Thus, the amount of bilirubin in the normal serum is 0.2 to 0.6 units or a dilution of 1 to 3 mg. per liter.

The dilution of the serum in the quantitative test must be taken account of. Van den Bergh says that if 0.5 cc of serum is precipitated with 1 cc of alcohol and centrifuged the supernatant fluid is $\frac{10}{7}$ cc, or 1.43 cc. The amount of pigment left in the precipitate is not considered. The amount of bilirubin in the 0.5 cc of serum is now in the $\frac{10}{7}$ cc of supernatant fluid, and so is in a dilution of $\frac{20}{7}$. To 1 cc of this supernatant fluid is added 0.25 cc of diazo solution and 0.5 cc of alcohol making this dilution $\frac{7}{4}$. Thus the total dilution is:

$$\frac{20}{7} \times \frac{7}{4} \text{ or } 5$$

The final reading must therefore be only one-fifth of the actual amount present and must be multiplied by 5. The amount of pigment left in the precipitate is ignored. It is greater in amount in cases of obstructive jaundice to judge from the color.

In carrying out the method the writer has found that there are several important points: (1) The reagents must be fresh and of good quality (considerable difficulty occurred when sulphanilic acid, which had been in stock for some time, was used); (2) the solutions must be made up fresh after the time mentioned for each has passed; (3) the glass tubes which are used must be clean.

A number of sera were examined immediately after collection of the blood and also after twenty-four hours in the ice box. In no case was any change found in either the direct or indirect reaction. At room temperature there was a diminution in the bilirubin content after twenty-four hours. Plasma from oxalated blood was examined, using the serum as a check in several cases and the same reading obtained. In the cases here recorded the tests in most instances were made within two hours of the collection of the blood. Occasionally the specimens had been kept on ice.

Slight hemolysis does not interfere with the readings. To a number of samples of blood enough distilled water was added to cause a distinct pink color in the serum. Allowing for the dilution, these sera gave the same reading as the non-hemolyzed controls. Almost all sera will give some color in the indirect reaction. Occasionally a normal serum gives a color too slight to read, that is; less than 0.2 units or 1 mg. of bilirubin per liter, but the writer has seen only two specimens with no trace of color. The addition of the 0.5 cc of alcohol after adding the diazo solution will clear up any opacity which may be present. Any serum having a positive direct reaction will have a positive indirect reaction but the reverse is not true.

Interpretation of the Test. The direct test may result in one of three ways:

1. The immediate direct: When this reaction occurs the bilirubin is believed to be present in the form in which it occurs in the bile, hence an obstructive jaundice is indicated. In 7 cases of common duct stone, and in 7 cases of occlusion of the common duct by tumor or pancreatic disease, the immediate direct reaction occurred.

2. The delayed direct reaction and the negative direct reaction must be grouped together clinically, for either may occur when there is increased bilirubin of the non-obstructive or hemolytic type. In the anemias, in chronic cholecystitis, and usually in the infective or toxic jaundices, the reaction is of this type.

2. The biphasic reaction is apparently a combination of the two preceding reactions. There is an immediate direct reaction with later developing increase of color. The biphasic reaction occurred in this series in 2 cases of pneumonia with jaundice, 1 case of catarrhal jaundice, and 1 case of cirrhosis. It is well to point out that the absence of a biphasic reaction does not mean that only bilirubin of the obstructive form is present, for often the hemolytic form of bilirubin is present but gives no reaction by the direct method.

The amount of bilirubin present, as determined by the indirect reaction, does not determine the presence or absence of the delayed reaction, for a high indirect reading was in several instances accompanied by an absent direct reaction.

Three forms of bilirubin must therefore be distinguished: That giving the immediate direct reaction, that giving a delayed direct reaction and a third which gives no direct reaction. All three react in the presence of alcohol and give a positive indirect. The delayed direct and absent direct cannot be separated in their clinical significance, for in every pathological condition in my series of cases in which one occurred the other was also observed in 1 or more cases.

That there is a distinct difference between the obstructive pigment and the hemolytic there can be no doubt. Andrewes⁹ recently has been able to demonstrate other differences than that of their reaction to the diazo reagent, but the fundamental reason for these differences is as yet unknown.

The indirect reaction is purely quantitative. All forms of bilirubin apparently react to it. The normal serum has been found to contain bilirubin in a concentration of from 1 to 3 mg. per liter, or, in terms of units, from 0.2 to 0.6 unit.

The ability to detect small amounts of bilirubin in the serum has made possible the recognition of latent jaundice and of increases or decreases in the amount of bile pigment in the blood of a patient.

Results. The results in this series of cases of chronic cholecystitis do not confirm the findings of some investigators, for 7 of the 9 cases are well within normal limits—1 is top-normal (0.6), while only 1 is above this figure. Friedman and Straus,¹⁰ who report a series of cases of cholecystitis, using the van den Bergh reaction but without making a quantitative test for bilirubin, considered any serum giving a definite pink tint in the indirect reaction as pathological. Many sera from normal individuals have a bilirubin content of 0.4 to 0.6 unit and this means that there is a definitely pink color with the diazo reagent. A quantitative figure below 0.6 unit certainly cannot be considered abnormal.

Evarts Graham and his associates¹¹ have shown the relationship between hepatitis and cholecystitis. In their opinion many of the cases of cholecystitis are the result of a primary hepatitis, the liver being usually infected through the portal circulation. Since the lymphatics of the liver and gall bladder communicate with each other a primary cholecystitis may result in a secondary hepatitis, but the gall bladder may be infected primarily without extension of the process to the liver. Thus the results of the van den Bergh reaction may vary, depending upon the degree of hepatitis associated with a cholecystitis. The cases in which hepatitis accompanies the cholecystitis may explain the increase in the bilirubin of the indirect test. If the cholecystitis is primary and the liver damage slight no evidence of the latter will be found by this test.

In the cases of chronic calculus cholecystitis without obstruction of the common duct it is probable that the infection has persisted for a longer period and has so affected the hepatic cells as to cause definite damage with retention of pigment and hence high values for the indirect reaction. Of the 11 cases in this series 5 were definitely high, 3 were top-normal and only 3 were well within normal limits.

As would be expected, the cases of common duct stone,⁷ and those of occlusion of the common duct by tumor or pancreatic disease,⁷

showed high values in the indirect reaction and an immediate direct reaction due to the obstruction to the outflow of bile and consequent readmission into the blood of bile pigments.

TABLE I.

	Indirect units.	Direct.
Chronic cholecystitis	0.2	Negative
	0.2	"
	0.2	"
	0.3	"
	0.3	"
	0.4	"
	0.5	"
	0.7	"
	0.6	Delayed
Chronic calculus cholecystitis	0.2	Negative
	0.4	"
	0.5	"
	0.6	"
	0.9	"
	1.0	"
	0.6	Delayed
	0.6	"
	0.8	"
	1.1	"
	1.9	"
Acute cholecystitis	0.6	Negative

TABLE II.

	Indirect units.	Direct.
Common duct stone	2.1	Immediate
	5.0	"
	5.0	"
	5.0++	"
	8.0	"
	8.0	"
	9.0	"
Occlusion of common duct by tumor or pancreatic disease	3.6	Immediate
	18.0	"
	5.0++	"
	5.0++	"
	9.8	"
	1.4	"
	5.0	"

In pneumonia the direct reaction shows variations of especial interest. As will be seen from Table III, the majority of cases gave a delayed or negative direct reaction with, in 1 case, a bilirubin concentration as high as 25 mg. per liter (5 units). In 2 cases a biphasic direct reaction was present and in only 1 an immediate direct reaction. It is possible in the last case that the very strong immediate reaction masked a less-marked delayed one. These delayed and negative reactions point to either an active hemolysis or to a toxic condition of the liver which interferes with its normal

action upon the bile pigment. In the 3 cases with biphasic and immediate reactions reabsorption of bile has certainly occurred if we accept van den Bergh's interpretation of the immediate direct reaction.

TABLE III.

	Indirect units.	Direct.
Pneumonia	5.0+	Immediate
	9.5	Biphasic
	2.2	"
	1.0	Delayed
	5.0	"
	1.5	"
	0.75	"
	0.6	Negative
	1.4	"

The difference in the quantitative readings between the severe secondary anemias and the cases of pernicious anemia is striking.

TABLE IV.

	Indirect units.	Direct.
Primary pernicious anemia	0.4	Negative.
	0.6	"
	0.6	"
	0.7	"
	0.8	"
	0.8	"
	0.9	"
	1.1	"
	1.1	"
	1.2	"
	1.5	"
	1.7	Delayed
	1.9	"
	4.0	Negative.
Primary pernicious anemia (?)	0.2	Negative.
	0.6	"
	0.7	"
	1.0	"
Secondary anemia	0.2	Delayed
	0.2	Negative.
	0.2	"
	0.2	"
	0.2	"
	0.2	"
	0.2	"
	0.2	"
	0.2	"
	0.2	"
	0.2	"
	0.3	"
	0.3	"
	0.4	"
Hemolytic ictero-anemia	0.5	"
	0.6	"
	1.5	Negative.
	2.1	"
	2.5	Delayed
	4.0	Negative.
Leukemia	±0.2	Negative.
	±0.2	"
	±0.2	"
Purpura hemorrhagica	0.0	Negative.

All except one of the readings in pernicious anemia were top-normal or above normal, one as high as 4 units. In the secondary anemias, on the other hand, 9 of the 14 cases had 0.2 unit, the lowest reading possible; 2 had 0.3 and only 1 was as high as 0.6. Whatever the cause, bilirubin is increased in the blood in the primary anemias, and present in normal amounts in the severe secondary anemias.

The quantitative readings in the cases of cardiac decompensation are of interest, for of the severe cases 4 were definitely high, 1 was top-normal, while only 2 were well within normal limits. The direct reactions were either delayed or negative. The hepatic involvement commonly found in cardiac decompensation might well account for this increase of the pigment.

TABLE V.

	Indirect units.	Direct.
Catarrhal jaundice	19.5	Biphasic
	4.1	Immediate
	5.0 + +	"
	2.0	Delayed
	1.8	"
	3.1	"
Cirrhosis	5.0	"
	0.6	Negative
	0.45	"
	0.4	"
Carcinoma of liver	2.5	Biphasic
	0.2	Negative
	0.5	"
	0.5	"
	2.0	"
Arsphenamin toxemia	0.8	"
	1.2	Delayed
Cardiac decompensation	0.4	Slightly delayed
	0.4	"
	0.6	"
	1.1	Delayed
	1.2	"
	1.2	"

Summary. The test of van den Bergh for the estimation of the type and quantity of bilirubin found in the blood serum is discussed, as is also his interpretation of the test and the theories on which he bases his interpretation. Whether van den Bergh's theory of jaundice is accepted or not, the test and his interpretation of it are in accord with the clinical findings in a series of over 100 cases. Normal results range from 0.2 to 0.6 unit, the majority of readings being 0.2 to 0.3.

In 14 cases of occlusion of the common duct by stone, tumor or pancreatic disease, a strong immediate direct reaction was obtained and the indirect reading ranged from 1.4 to 18 units.

Serum from 9 patients with chronic cholecystitis gave only the delayed or negative direct reaction, and the indirect reaction gave a value above normal in only 1 case. Eleven cases of chronic calculus cholecystitis gave negative or delayed direct reactions, with indirect readings from 0.2 to 1.9 units.

In 14 cases of secondary anemia the indirect result was always within the normal range. In 14 cases of pernicious anemia the bilirubin in the serum was high, from 0.7 to 4 units in 11 cases; 0.6, or top-normal, in 2 cases; well within normal limits, 0.4, in 1 case.

Four cases of hemolytic ietero-anemia showed a greatly increased amount of bilirubin of the hemolytic type, in the serum, 1.5 to 4 units. In 3 cases of leukemia and 1 of purpura hemorrhagica low normal values were obtained.

Conclusions. The van den Bergh test for bilirubin in the blood serum in this series of over 100 cases has given results which are in accord with the clinical picture. These tests differentiate consistently between the jaundice of obstruction and of hemolysis.

They are tests for liver function only in so far as they indicate alteration in bile pigment metabolism.

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THE THYROXIN AND TRYPTOPHANE CONTENT OF THE DISEASED THYROID GLAND, AND THE IODIN COMPOUNDS IN DESICCATED THYROID.*

BY JAMES F. WEIR, M.D.,

DIVISION OF MEDICINE, MAYO CLINIC AND MAYO FOUNDATION, ROCHESTER, MINN.

WHEN the thyroid gland is boiled with dilute sodium hydroxide, and is then made acid, about 50 per cent of the total iodine present is found in the precipitate and 50 per cent is soluble in the presence of mineral acid. The soluble iodine compounds do not possess any demonstrable physiological activity, and it is difficult to conceive

* Work done in the Section on Biochemistry, The Mayo Foundation, submitted for publication, January 27, 1925.

of any chemical procedure by which they could be altered to produce thyroxin. The acid insoluble material contains all of the thyroxin which is present after boiling with alkali. Whether this is a measure of the total amount originally present cannot be determined. A large percentage of the iodine in this fraction can be separated as thyroxin without further alteration. This procedure, therefore, is a possible method of estimating the relative content of thyroxin in various samples of thyroid material.

The method which has been used is to boil, under a reflux condenser, 10 gm. of finely ground, fresh goiter tissue removed at operation, with 4 per cent sodium hydroxide for fifteen minutes, then to remove a sample, continue boiling for one hour, to remove a second sample, and continue boiling for two hours. The various samples are then treated with acid and filtered. Acid is added to precipitate thyroxin, which is insoluble in neutral or acid solutions. Iodine is determined in the solution before precipitation, and in the filtrates, by the method developed by Kendall. Samples of desiccated thyroid were similarly treated.

The author studied the goiters in a series of 37 cases, consisting of 24 of parenchymatous hypertrophy (exophthalmic goiter) and 13 adenomatous glands (Table I). The cases of exophthalmic goiter are considered first, and in the order of increasing total iodine content. Then follow cases of adenomatous goiter in the same order and without considering the presence or absence of clinical symptoms (Table II).

Wilson and Kendall have shown that in normal glands approximately 50 per cent of the total iodine is stable in boiling alkali, and is acid-insoluble. In cases of adenomatous goiter this percentage may or may not be changed. In the small series considered here the average was 52 per cent; the extremes, 15 and 66 per cent. This average is considerably higher than that reported by Wilson and Kendall, their percentage being 30 in cases with hyperthyroidism, and 34 in cases without hyperthyroidism. Neither from the thyroxin content nor total iodine content could any indication of the presence or absence or severity of hyperthyroidism be obtained. It is interesting to note, however, that in all cases in which there was high total iodine content the goiter was described by the pathologist as colloidal in type.

The hyperplastic (exophthalmic goiter) glands, as shown by Wilson and Kendall, present two changes: Low total iodine content and a low percentage of total iodine as thyroxin iodine. In their series of cases the total iodine was 0.11 per cent (1.1 mg. in each gram.), and the average thyroxin content was 28 per cent. In the 24 cases of exophthalmic goiter the average total iodine was 0.26 per cent (2.58 mg. in each gram), of which an average of 43 per cent was thyroxin iodine. Thus not only is the total iodine much higher, but also the percentage in the form of thyroxin is

materially increased. The difference in these percentages is undoubtedly due to the administration of iodine (Lugol's solution)⁴ to all such patients over a variable length of time prior to operation. Thus we have a chemical criterion which agrees with the general clinical improvement of the patient.

TABLE I.—IODIN CONTENT OF GOITERS.

Case.	Diagnosis.	Basal metabolic rate.	Iodin and tryptophane in each gram of dried gland.			
			Total iodine, mg.	Iodin, stable after boiling, mg.	Iodin, stable (thyroxine), per cent.	Tryptophane, mg.
1	Exophthalmic goiter . . .	+79	0.86	0.18	20	21.4
2	Exophthalmic goiter . . .	+51	1.04	0.33	32	15.4
3	Exophthalmic goiter with adenoma	+73	1.25	0.40	32	
4	Exophthalmic goiter . . .	+57	1.36	0.37	27	
5	Exophthalmic goiter . . .	+31	1.36	0.54	40	26.4
6	Exophthalmic goiter with thyroiditis	+49	1.36	0.63	47	
7	Exophthalmic goiter . . .	+26	1.45	0.15	10	
8	Exophthalmic goiter	1.80	0.70	39	
9	Exophthalmic goiter with adenoma	+28	1.90	0.30	15	
10	Exophthalmic goiter with adenoma	+49	1.91	0.70	38	
11	Exophthalmic goiter . . .	+39	2.15	1.25	58	35.0
12	Exophthalmic goiter . . .	+62	2.40	1.20	50	38.0
13	Exophthalmic goiter . . .	+90	2.41	1.00	42	
14	Exophthalmic goiter . . .	+38	2.72	0.83	31	26.6
15	Exophthalmic goiter with adenoma	+33	2.72	1.80	62	
16	Exophthalmic goiter . . .	+76	2.90	1.20	42	19.0
17	Exophthalmic goiter	2.90	1.55	54	33.2
18	Exophthalmic goiter . . .	+100	3.30	1.75	53	41.6
19	Exophthalmic goiter . . .	+62	3.33	1.30	39	
20	Exophthalmic goiter . . .	+78	3.45	1.82	53	33.2
21	Exophthalmic goiter with adenoma	+55	3.50	2.10	61	
22	Exophthalmic goiter . . .	+38	3.80	2.75	73	28.5
23	Exophthalmic goiter . . .	+84	5.73	2.95	52	33.3
24	Exophthalmic goiter . . .	+84	6.25	3.80	61	33.3
25	Adenoma with hyperthyroidism	+19	0.31	0.19	63	34.2
26	Non-toxic adenoma . . .	- 1	0.39	0.06	15	
27	Non-toxic adenoma . . .	0	0.72	0.45	63	
28	Adenoma	0.77	0.19	25	38.4
29	Toxic adenoma	+21	0.96	0.42	44	
30	Toxic adenoma	+35	1.05	0.33	32	
31	Toxic adenoma	+44	1.28	0.56	48	
32	Toxic adenoma	+31	1.32	0.64	49	
33	Toxic adenoma	+56	1.94	1.19	61	31.3
34	Adenoma in colloid thyroid	+19	2.58	1.16	45	33.1
35	Adenoma in colloid thyroid	+31	3.25	1.70	53	33.3
36	Toxic adenoma	+26	3.27	1.96	60	40.4
37	Toxic adenoma	+47	3.65	2.40	66	

TABLE II.—SUMMARY AND AVERAGES OF IODIN IN GOITERS.

Type of cases.	Cases.	Average basal metabolic rate.	Iodin and tryptophane in each gram of dried gland.			
			Total iodine, mg.	Iodin as thyroxine, mg.	Iodin as thyroxine, per cent.	Tryptophane, mg.
Exophthalmic goiter . . .	24	+56	2.58	1.11	43	29.6
Adenoma	13	+27	1.65	0.86	52	35.1

No relationship could be established between the basal metabolism and the thyroxine content.

Because of the close structural relationship between thyroxine and tryptophane it was thought that a determination of the latter might show changes in pathological conditions. The method employed was that of May and Rose, depending on the development of a blue color with dimethylpara-aminobenzaldehyde. Casein was used as a standard, and calculations were based on casein containing 2 per cent of tryptophane. The determination was carried out on 52 glands removed at operation (Table III). The average content was 29.6 mg. in each gram of dried tissue (approximately 3 per cent). On classifying these glands according to the type of disease, clinically or pathologically, no characteristic variations are found. Furthermore, no relationship could be established between the content of thyroxine or tryptophane or the basal metabolic rate.

TABLE III.—TRYPTOPHANE CONTENT OF THYROIDS.

Milligrams in each gram.	Cases.	Exophthalmic goiter.	Adenomatous goiter.
10 to 15	2	2	
15 to 20	5	5	
20 to 25	7	4	3
25 to 30	14	10	4
30 to 35	14	7	7
35 to 40	5	4	1
40 to 45	4	1	3
45 to 50	1	..	1
Total	52	33	19
Average content	29.6	27.5	33.0

The Iodin Compound of Desiccated Thyroid. A specimen of desiccated thyroid was used in these experiments. Two grams were dissolved in 100 cc of water and 20 cc of 20 per cent sodium hydroxide and boiled under a reflux condenser for varying lengths of time. The specimens were then removed, neutralized with sulphuric acid, and the precipitate filtered off. It was necessary to add 200 to

300 mg. of an organic acid to the solution in sodium hydroxide before neutralizing with acid. This organic acid was insoluble in acid and would flocculate the precipitate prior to filtering. If tungstic acid instead of sulphuric acid was used, this procedure was unnecessary. Iodin was determined in the filtrates. The total iodine was 2.8 mg. in each gram. As boiling was prolonged, it was increasingly difficult to obtain a satisfactorily clear filtrate, even using tungstic acid as a precipitant (Table IV).

TABLE IV.—IODINE IN DESICCATED THYROID, SODIUM HYDROXIDE STABLE AND ACID INSOLUBLE.

Time in hours.	0.25.	1.	3.	9.
Milligrams iodine in each gram soluble in sulphuric acid . . .	0.8	1.0	1.5	1.3
Per cent of iodine soluble . . .	28.5	35.7	53.6	46.4
Per cent of iodine stable in sodium hydroxide	71.5	64.3	46.4	53.6

From these figures we see that, on an average, 50 per cent of the iodine in desiccated thyroid is stable in boiling sodium hydroxide, and is insoluble in acid. Thyroxine is the chief constituent of this portion. Further decomposition of the iodine compound is not obtained by boiling for periods longer than three hours.

It is difficult to determine whether the iodine is present as an organic iodine compound or as sodium iodide after boiling in sodium hydroxide. However, the nitrous acid test gives some information. Three grams of desiccated thyroid were boiled in sodium hydroxide for one hour, cooled, treated with tungstic acid and filtered. The filtrate was evaporated to less than 10 cc, and then nitrous acid and starch were added. A good trace of blue color appeared; however, not more than was obtained with 0.1 mg. iodine in the form of sodium iodide. After boiling 3 gm. of desiccated thyroid for one hour, at least 3 mg. of iodine is soluble in mineral acids. If this was present as sodium iodide a very strong nitrous acid test would have been obtained. Evidently, therefore, the compounds which are acid-soluble contain iodine, and only a very small amount (less than 5 per cent) of the total iodine is broken off as inorganic iodides. These results show that the iodine in the thyroid is practically all in organic combination; about 50 per cent is insoluble in acid and 50 per cent is soluble in acid after the gland has been boiled in 4 per cent sodium hydroxide.

Summary. From the synthetic work with thyroxine, it appears impossible to alter any compound which could be called a precursor of thyroxine into thyroxine by treatment with alkaline hydroxide.

In the normal gland the amount of total iodine present in a form stable to sodium hydroxide (thyroxine) is approximately 50 per cent of the total iodine.

In the exophthalmic goiter the total amount of iodine present is

less than normal, and the percentage of the total which is in the form of thyroxin is very materially reduced.

After administration of Lugol's solution the total amount of iodine in the exophthalmic goiter increases, and the percentage in the form of thyroxin increases. These changes parallel the clinical improvement in the patient.

There is no apparent relationship between the thyroxin content of the thyroid and the basal metabolic rate.

Tryptophane exists in the thyroid in rather high percentage, an average of 3 per cent, but no definite relationship was found between this and the type of gland pathologically, the thyroxin content or the basal metabolic rate.

The iodine which is soluble in acid after the gland has been digested with sodium hydroxide is not present as inorganic iodide, but is still organically combined.

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THE USE OF LIPIODAL IN THE LOCALIZATION OF SPINAL LESIONS.

A PRELIMINARY STUDY.

BY FRANKLIN G. EBAUGH, A.B., M.D.,

DIRECTOR, COLORADO PSYCHOPATHIC HOSPITAL, DENVER, COLORADO.

(From the Neuropsychiatric Department, Philadelphia General Hospital, Philadelphia.)

THE use of lipiodal (iodized poppy oil), since its introduction by Sicard,¹ has been of great diagnostic value in the localization of spinal block, thereby paving the way for early operation in cases of spinal cord tumors. Ayer's² work regarding puncture of the cisterna magna and his elaboration of combined cisternal and lumbar punctures has made possible the diagnosis and demonstration of spinal subarachnoid block from any cause, but does not give accurate localization. The intracistern injection of iodized oil

combined with roengenographic studies will show location of spinal blocks. It is the purpose of this paper to report briefly 3 cases in which lipiodal was of great value in localization. In 2 cases its use led to operation, in which the findings of spinal block were verified. In another case the findings were negative and saved the patient from a possible laminectomy. We also wish to comment briefly upon the reactions following the injection of iodized oil, and the need for further observations concerning its routine use combined with roentgenographic studies.

Case Reports and Comment. CASE I.—J. H. H., aged twenty-five years, was transferred from the medical service, May 7, 1924, to the neurological service of the Philadelphia General Hospital, of Drs. Charles Potts and J. W. McConnell. He had had pneumonia January, 1924, followed by empyema. An exploratory thoracotomy was performed April 30, 1924. At this time spinal anesthesia was unsuccessful and a diagnosis of spinal block suggested itself. Roentgenographic studies gave evidence of fluid in the left chest. Neurological examination showed paralysis of both legs. Atrophy of both legs was marked and sensory disturbances consisted of dysthesia for pain sense beginning with the first dorsal segment and becoming more marked at the level of the fifth dorsal segment and extending to the first lumbar segment. This dysthesia without definite level together with the history of lung infection and subsequent unsuccessful attempt to institute spinal anesthesia pointed to a diagnosis of diffuse myelitis more marked between the seventh dorsal segment and the first lumbar segment. A possibility of plastic exudate about the nerve roots could not be ruled out. During the patient's course in the hospital, two combined cisternal and lumbar punctures were performed. The following data were obtained:

COMBINED LUMBAR AND CISTERNAL PUNCTURE JULY 6, 1924.

	Cisternal data.	Lumbar data.
Initial pressure	60 mm.	60 mm.
Pulse variation	Good	Slight
Respiratory variation	Good	Slight
Increase on pressure over jugular, marked	60 mm. to 320 mm.	60 mm. to 70 mm.
5 cc fluid removed from lumbar	60 mm.	35 mm.
5 cc cisternal fluid removed	50 mm.	35 mm.
5 cc fluid from lumbar	50 mm.	0

Coughing and abdominal pressure caused a uniform increase in pressure in cisternal manometer with no change in lumbar region.

Cisternal fluid: Clear; no cells; globulin, slight increase; colloidal gold, 0001110000. Wassermann negative.

Lumbar fluid: Clear; heavy; globulin, increase; colloidal gold, 5555555422. Wassermann negative.

Diagnosis of subarachnoid block was made.

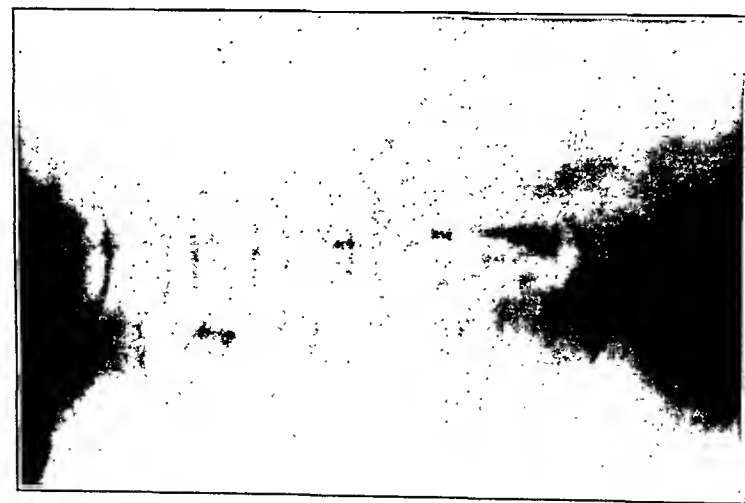


FIG. 1.—Taken one hour after injection, showing iodized oil extending from first to fifth dorsal vertebra.

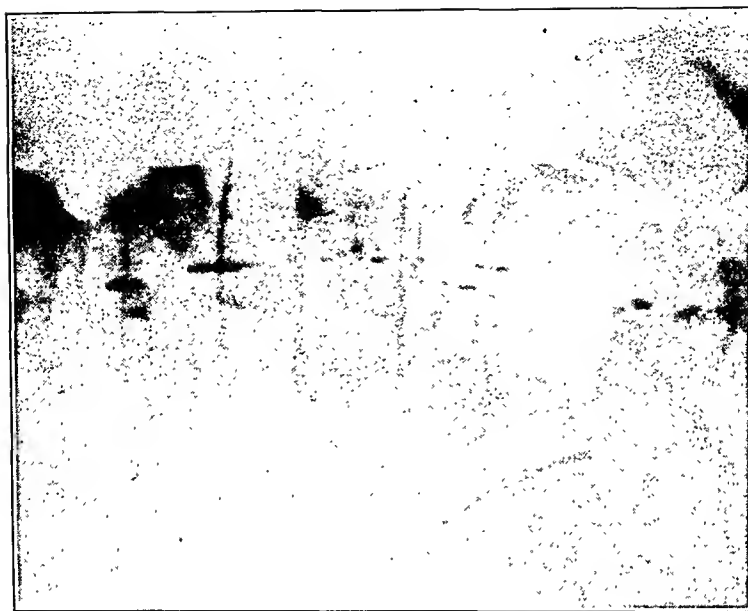


FIG. 2.—Showing location of iodized oil six hours after injection.



FIG. 3.—Showing position of iodized oil eighteen hours after injection.



FIG. 4.—Showing iodized oil at the lowest level in the subarachnoid system, demonstrating that no block was present.



FIG. 5.—Showing iodized oil at the fifth dorsal vertebra, corresponding to site of neurological diagnosis.

Combined puncture was repeated July 28, 1924, with similar readings. At this time 2 cc of lipiodal was injected in the cisterna magna. On the basis of the two double punctures a diagnosis of spinal block was made. A diagnosis of complete spinal block was not definite because in each case there was some change in the lumbar monometer on pressure over the jugulars, which we have not noticed previously in complete blocks. The roentgenographic reports* following the injection of lipiodal were as follows: The initial film (Fig. 1) taken one hour after injection shows "more than one column of the opaque material—one to the right of the spines of the vertebra extending from the first to the fifth dorsal, on the left from the first to the third dorsal. There is none of the oil below these points." Films made six hours later (Fig. 2) show "injected material on each side of the spine first and second dorsal, and disintegrated particles along the right of the spine from the first lumbar to the sacrum." The films made eighteen hours later (Fig. 3) show "similar appearances of dorsal region as in the first one made. The lumbar vertebra are similar to the second film except there is more of the oil at the sacrum." Previous roentgen-ray examinations of the spine were negative. The laboratory reports on two occasions showed negative fluid and spinal fluid Wassermann. The colloidal curve was 345555532. Blood chemistry and other studies were negative.

A laminectomy was performed August 19, 1924, by Dr. Francis Grant under ether anesthesia. The spines of the fourth, fifth and sixth dorsal were removed. Outside of the dura considerable fluid was found. On rinsing, the dura was found to be directly against the cord without any intervening fluid. It is interesting that these findings corresponded closely to those of the initial plate, in which the iodized oil tended to localize at the fifth dorsal vertebra (Fig. 1).

This case was an extremely confusing one and the value of the use of lipiodal combined with double puncture is illustrated, the final operation showing a diffuse adherent inflammatory exudate about the spinal cord as localized by lipiodal and roentgenographic studies. The findings of complete block by the use of double puncture were also verified at operation.

Case II† may be briefly discussed, since the opinion that there was no spinal block present was confirmed following the injection 3 cc of lipiodal into the cisterna magna. The above film taken shortly after the injection shows that all the iodized oil has reached the base of the spinal sac (Fig. 4). This case was a confusing one in that at first many signs pointed to a spinal cord lesion in the lower cervical region. A diagnosis of epidemic encephalitis with radiculitis was made and has been confirmed by the later develop-

* The studies were made by Dr. Holmes of the Philadelphia General Hospital Roentgen-ray Laboratories.

† Service of Dr. C. A. Heiken of the Misericordia Hospital.

ment of a paralysis agitans syndrome. The use of lipiodal in this case not only decided the diagnosis, but probably saved the patient from an exploratory laminectomy, which would have been justified without the use of this method.

Case III is of extreme interest in that combined cisternal and lumbar puncture was not completed owing to inability to obtain fluid from the lower region. Previously the report showed a yellow fluid containing three cells with a heavy cloud of albumin. Repeated neurological examinations in this case showed evidence of localization of the tumor at the fifth dorsal vertebra. A definite diagnosis of spinal cord tumor was made, since all other diagnostic possibilities were ruled out after detailed studies. The patient had the typical sensory and motor symptoms at onset. A sensory impairment corresponding to the seventh spinal segment was evident. All laboratory examinations were negative. The Queckenstedt test showed that there was no increase in cerebrospinal fluid pressure in the lumbar area. The pressure determinations and variations in the cisterna magna were normal. Two cc of the iodized oil were injected in the cisterna magna and films taken shortly afterward showed definite localization at the fifth dorsal vertebra (Fig. 5). On April 23, laminectomy was performed by Dr. Rodman and a tumor was removed from the above location. This tumor was located on the anterior surface of the cord and was approximately 4 cm. in length. Gross appearance was that of a neurofibroma, which readily separated from the cord.

This case was interesting in that following the lipiodal injection the patient complained of pain in the seventh spinal segment and localized sweating over the adjacent vertebra was present. These phenomena disappeared twenty-four hours after the injection. On the basis of reports by Laplane³ this pain is significant and arises apparently in the sensory roots at the point of lesion. These findings are, therefore, of clinical import and frequent neurological examinations after lipiodal injection should be made. In this preliminary report we were interested in the apparent absence of other reactions following the injection of iodized oil. There were no definite reactions. The patients objected to repeated punctures and we were unable to follow possible cytological changes following the injection of lipiodal. At present there are no reports in American literature available except the work of Ayer and Mixter⁴ and this case report by Russell.⁵ The work of Ayer and Mixter indicated that lipiodal causes irritation and they feel this method is not for indiscriminate use. Careful studies of spinal fluid cytology should be made as well as quantitative globulin determinations. Roentgen-ray films made several days after injection of the oil showed that there was no change in position and that the oil gravitated to the lowest point possible. Careful postmortem studies should be made regarding the possible demonstration of inflammatory reactions. In the future fluoroseopical studies should prove

interesting and should enable one to determine the time required for the passage of the oil from the cisterna magna to the sacrum, as well as the best position in which to take roentgenograms. In our studies the sitting position was used in each case. Laplane prefers the lateral decubitus on an incline, which he feels is more favorable for the passage of the oil. The application of this method should clarify and differentiate many confusing spinal lesions, particularly brought up by the question of spinal caries and extradural and intradural pressure of any type. Since it is clearly established that the operability of spinal cord tumors is much higher than that of brain tumors it is desirable that an early diagnosis be made. The use of iodized oil should result in the establishment of early diagnosis and, therefore, early operation. Frazier and Spiller⁶ report the average time of two and two-fifths years before the diagnosis of spinal cord tumors is made. The further use of lipiodal in various inflammatory conditions, particularly of postmeningitic origin should prove of extreme value. On reviewing many cases of epidemic encephalitis we have examined, we cannot help but feel that lipiodal would have given us valuable clinical observations in this group of cases. At least its use would have prevented a laminectomy in one difficult case that came to the author's attention.

Summary and Conclusions. The injection of lipiodal, with accompanying roentgenographical studies, is of definite value for the accurate localization of spinal cord block. In spinal cord tumor the use of lipiodal should lead to earlier operation and in this preliminary study of 3 cases we feel its use may be further indicated to be of value in acute inflammatory conditions, such as may arise in the treatment of, or following epidemic meningitis (subarachnoid spinal block). There were no marked subjective reactions experienced in the use of lipiodal. Further studies regarding the evidence of inflammatory changes and cytological investigations of the spinal fluid will be necessary. It is logical that lipiodal should always be injected into the cisterna magna since it gravitates and seeks the lowest level and thereby localizes at any site of obstruction.

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**AN INSTRUMENT UTILIZABLE FOR VARIOUS OPERATIONS:
BLOOD TRANSFUSION, HYPODERMOCLYSIS, INTRAVEN-
OUS INFUSION, PHLEBOTOMY AND WITHDRAWAL
OF FLUIDS FROM BODY CAVITIES.**

BY HENRY M. FEINBLATT, M.D.,
BROOKLYN, N. Y.

(From the Clinical Laboratory, United-Israel Zion Hospital, Brooklyn, N. Y.)

In a previous communication the author¹ described a new and simple form of apparatus for the performance of blood transfusion by the vein-to-vein method. This instrument, it is believed, reduces the difficulties of manipulation to a minimum, and at the same time obviates the possibility of a reflux of blood from the recipient to the donor. The machine consists essentially of two disks rotating one upon the other through an angle of 90 degrees, the range of motion being limited by a stop-regulator. The proximal disk is perforated to form a channel for communication with a 20-cc Record syringe; this opening may, by rotating the disks, be made to become alternately continuous with either of two similar openings in the peripheral disk for the inlet and outlet respectively. The inlet and outlet tubes are connected, one with the donor and the other with the recipient. The machine, with the inlet and outlet projecting upward, may be held in a slotted holder, which is clamped to the table.

The purpose of this report is to call attention to some additional diagnostic and therapeutic procedures for which this instrument may conveniently be employed. In general, where it is desired to remove fluid from a patient, or to inject liquid or air, the use of this apparatus would appear to be applicable. The machine has been tried clinically and found to be useful in the following therapeutic and diagnostic procedures: (1) Hypodermoclysis, when it is desired to introduce a large amount of fluid in a short space of time; (2) intravenous infusion; (3) phlebotomy; (4) removal of fluid from the chest and abdominal cavities. In addition, several experiments on animals have indicated that a simple method of inducing artificial pneumothorax may be available by the use of this apparatus, but the author is not yet prepared to report finally upon this application.

Hypodermoclysis. The author's blood-transfusion apparatus offers a ready means of introducing considerable quantities of fluid under the skin within a short period of time. Fluids, and water in particular, are readily absorbed from the submammary

¹ Feinblatt, H. M.: A Simple Apparatus for Blood Transfusions, *Med. Jour. and Record* (awaiting publication).

region, the axillæ or the flanks, and it has been found that a subcutaneous injection of 500 cc can be very rapidly made.

The apparatus (Fig. 1), in addition to the transfusion instrument, consists of a 500- or 1000-cc flask, plugged with a cotton stopper around which passes a rubber tube to enter the bottle. This tube is connected with one of the terminals of the instrument by means of an adapter. The other terminal is connected directly with the needle. When it is desired to use both breasts or axillæ simultaneously, a Y-shaped connection may be utilized. The hypodermic needle should be about 3 inches long, preferably a gauge No. 18.

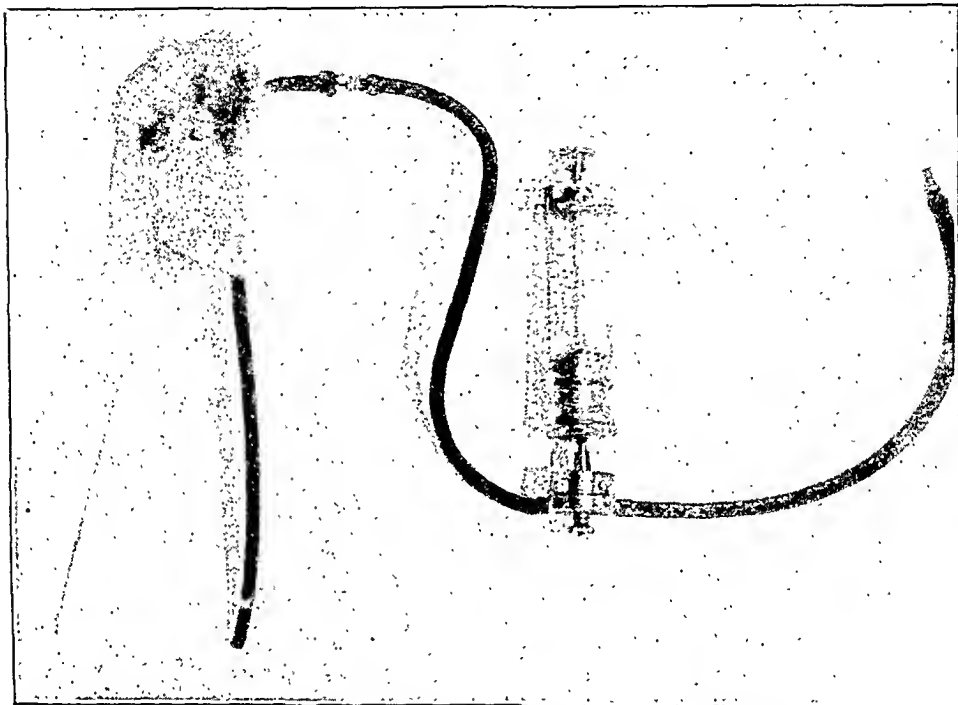


FIG. 1.—The author's transfusion apparatus adapted to the performance of hypodermoclysis.

The operation is exceedingly simple. All that is necessary to transfer the communication from the receptacle to the patient, and *vice versa*, is to rotate the disks one upon the other. The instrument is turned so that the inlet, that is, the opening in continuity with the receptacle, communicates with the syringe, and the piston of the latter is withdrawn, filling the syringe with the fluid. The disks are then rotated so as to connect the syringe with the outlet, and the syringe is emptied.

The speed of the injection is guided by the rate of absorption, as evidenced by the amount of swelling and the degree of pain induced. Bartlett² has shown that the addition of novocain to the solution in such amount as to produce a concentration of 0.0625 per cent

* Painless Hypodermoclysis, Ann. Surg., 1921, 73, 161.

renders hypodermoclysis perfectly painless and is at the same time safe. When continuous hypodermoclysis is required, the gravity method should be employed.

Artificial Pneumothorax. Artificial pneumothorax was induced in 2 normal guinea-pigs and 1 healthy dog, injecting 40 cc of air into the such of the former animals and 120 cc into the latter. A water manometer, which could be disconnected by means of a clamp, was connected with the proximal tube of the instrument, so as to indicate, by the negative pressure induced, the entry of the needle into the pleural cavity. Ordinary atmospheric air was employed. Pneumothorax was thus successfully induced in the 3 animals, and there were no untoward results. The author is not prepared to express an opinion as the applicability of this method to man.

Summary. An apparatus is described which can conveniently be adapted to various therapeutic and diagnostic procedures, namely, blood transfusion, hypodermoclysis, intravenous infusion, phlebotomy and the removal of fluid from the body cavities. It has also been successfully employed for the induction of artificial pneumothorax in animals. The simplicity of the instrument, its ease of manipulation and the certainty with which a one-way flow is established commend its use for these operations.

THREE UNUSUAL CASES OF BULLET WOUNDS OF THE HEART SHOWING ATTEMPTS AT HEALING.

By B. M. VANCE, M.D.,

ASSISTANT MEDICAL EXAMINER, CITY OF NEW YORK.

WHEN wounds of the heart were mentioned in the writings of classical antiquity and the middle ages, the inevitable fatality of these injuries was chiefly emphasized. The possibility of healing seems never to have been considered until J. Hollerius (1498 to 1562) advanced the theory that a spontaneous cure of a cardiac wound might occasionally occur. Later several observations were published which seemed to give support to his opinion.

As an example, J. C. Weber, about 1600, described a bullet encapsulated in the heart of a stag. Idonis Wolf, in 1642, tells of a soldier whose heart at autopsy showed a healed scar at the apex, presumably the result of a sword wound received four years previously. Henri ab Heers, in 1647, writes of a man who lived seven days after his heart had been penetrated twice by bullets. Similar cases continued to be published and it soon became evident that cardiac wounds were not invariably fatal.

George Fischer, in 1868,¹ was probably the first to make an extensive attempt to review the literature of this subject. He gathered together some 452 cases of which 401 were heart wounds and 51 involved the pericardium alone. He estimated that 30 per cent of the latter and 10 per cent of the former tended to undergo spontaneous cure. Fischer's statistics include all sorts of heart injuries.

For the purpose of greater convenience it is desirable to classify wounds of the heart, and accordingly we may separate them into four main divisions:

1. Injuries caused by non-penetrating blunt force applied externally.
2. Stab wounds and cutting wounds.
3. Injuries caused by foreign bodies other than missiles.
4. Missile wounds.

1. The injuries due to blunt force show a wide variation of anatomical lesion, as the force may be a tremendous one such as an automobile wheel that crushes in the chest, or a comparatively slight grade of violence as a plank thrown from a circular saw which strikes the breast sharply in the precordial region. In either event the force acts on the chest wall in such a way that the heart is either crushed, torn or ruptured and death occurs inevitably in the vast majority of cases. From the very nature of the injury the shock is usually of such extreme grade and the hemorrhage so severe that the patients do not respond to treatment.

2. Stab wounds and cutting wounds are caused by sharp pointed and sharp edged weapons, penetrating the heart (daggers, knives, hatpins, and so forth). The resulting injury may be a huge cut that causes death in a very few minutes from rapid hemorrhage, or it may be a small wound accompanied by so little shock and hemorrhage that ultimate recovery is not impossible.

3. The queerest category of cardiac injuries is that caused by foreign bodies other than missiles, a group which includes pins, needles, nails, toothpicks, glass splinters, false teeth, and so forth. These objects are supposed to reach the heart in three ways.

The first is by penetration of the chest wall in such a manner that the foreign body will either enter the heart muscle directly or temporarily lodge in the chest wall and finally reach the heart by "wandering." This latter process is supposed to be an attraction exerted on the object by the cardiac and respiratory movements, so that it is gradually drawn to the cardiac region. In general the foreign bodies that are subject to wandering are such objects as pins and needles which have a sharp point, a slender body, and a smooth surface (D. G. Zesas²).

The second way in which a foreign body can reach the heart is through the gastrointestinal tract. The heart is either penetrated directly through the pharynx, esophagus or stomach or, as in the case of Bailey,³ indirectly. Here the foreign body, a toothpick,

entered the inferior vena cava from the duodenum and was finally carried to the right auricle in the venous blood stream.

Buchanan,³ described a third method of approach in a peculiar case in which a needle was aspirated into the air passages and finally reached the heart through the right bronchus. This method, however, is rather rare.

The symptoms evoked by such foreign bodies vary greatly. Primary symptoms may be slight or absent, and the object may be encysted in the heart, remain quiescent during life and only be discovered accidentally at autopsy. In other cases the foreign body may give rise to alarming symptoms and cause death by hemorrhage and septic infection.

4. The heart may also be wounded by missiles or projectiles, which can be defined as foreign bodies driven to their objective by a force applied at a distance. For all practical purposes in our day these terms can be limited to objects propelled by explosives, such as bullets, shrapnel, shell fragments and the like. As the driving force behind projectiles is invariably tremendous, the wound of the heart is unusually severe and the resulting shock and hemorrhage are generally rapidly fatal. A high percentage of the cases die before surgical aid can be rendered.

The primary symptom of most bullet wounds of the heart is profound shock and collapse and the individual when shot generally falls, and is unable to move. Some exceptions occur. Cases have been recorded where an individual so injured was able to do some very surprising things. In the case of Th. Muller,⁴ for example, a fifteen year old boy climbed a flight of stairs immediately after his heart had been wounded by the bullet from a small caliber pocket pistol. Curran⁵ also tells of some very remarkable examples of a similar kind.

The complication which accompanies the shock is hemorrhage, which may be rapid and overwhelming or gradual and slow, depending on the size of the wound, the portion of the heart involved and numerous other factors. The bleeding at first extends to the pericardial cavity, then may involve the pleural cavity and only in a few instances exudes from the external wound or extends through the diaphragm. If the blood has no means of escaping from the pericardial sac death may ensue in a few minutes from compression of the heart or heart tamponade (a true example of asphyxia). Sometimes when the pericardial wound is so placed that the blood will find an outlet into one of the pleural cavities death may be postponed for many hours. The overflow into the pleura relieves the pericardium from a dangerous rise of internal pressure, and allows the patient to live until he finally dies from mere loss of blood. Recently the author saw such a case where a man aged twenty-one years, wounded in the left lung, the pericardium, the coronary venous sinus and both auricles by a 38 caliber lead bullet, was

enabled to survive these appalling injuries about twenty-four hours, simply because he had a wound of the pericardium that drained the blood into the left pleural cavity.

In those cases where the patient lives for a number of days death may be the result of a secondary septic infection, such as pericarditis, empyema, pneumonia or general sepsis of any variety. Sometimes the exitus is due to wounds of adjacent viscera as a pneumothorax which may complicate perforation of the lung or a peritonitis complicating an abdominal injury.

A large percentage of bullet wounds of the heart tend to heal up spontaneously and Fischer's¹ estimate of 10 per cent recovery under expectant treatment is generally considered correct. The readiness with which healing takes place depends on the nature of the cardiac injury. A large missile that traumatizes the muscle and leaves a gaping hole does not allow as much chance of successful healing as does a smaller projectile which causes a small wound, and so produces less shock and hemorrhage.

The location of the wound in the heart has a very important bearing on the prognosis. Wounds of the left ventricle have the lowest mortality, wounds of the right ventricle rank next, while wounds of the auricles are the most fatal of all. This is probably explained by the fact that the thicker ventricle muscle allows the projectile more readily to penetrate obliquely without cutting across the fibers, while the thin auricle wall is usually pierced rectangularly and the fibers cut crosswise, so that the bleeding is less likely to be checked. A missile that penetrates the heart cavity or pierces a large coronary artery is much more dangerous than one that involves the myocardium alone, for the same reason. Strangely enough a rather deadly type of bullet wound is that kind which ruptures the heart without penetrating the pericardium. The missile is often spent and stops just on the outside of the pericardium or it passes over the sac tangentially "creasing" the heart, but not entering the pericardial cavity. The mechanism is exactly similar to the rupture by blunt force.

Healing when it occurs takes place in the heart just as it does elsewhere in the body. The wound is first plugged by a blood clot which is later replaced by granulation tissue and then by scar tissue. The only difference, according to Anitschkow,² is the presence of a large cell with a peculiar nucleus which he called a myocyte, claiming that this cell is peculiar to granulation tissue in the myocardium. In any event, the result of the process is a dense fibrous callus which effectually closes the defect in the heart wall. However, even during healing a fatal accident sometimes occurs. In the early stages an increase in the intracardiac pressure may force apart the edges of the wound causing a secondary hemorrhage. If the wound is healed the same factor may cause the formation of a cardiac aneurysm at the site of the scar. In other cases one of the

valves may be injured and a stenosis and insufficiency result which might be the real cause of death. (Klose.⁷)

A large number of the cases which recover show the projectile embedded in the heart muscle enclosed by a fibrous capsule, and are often discovered quite by accident in the progress of an autopsy; for, like any other foreign body, when once encapsulated they rarely cause symptoms. Exceptions do occur, however, as in a case where the bullet by involving the bundle of His in the scar tissue gave rise to the symptoms of heart block. Aneurysm of the heart wall and adhesion of the heart to the pericardium may also result from the irritation set up by an embedded projectile (Klose⁷).

Sometimes bullets become attached to the endocardium or the pericardium. Riethus⁸ has described cases in which the bullet has entered the heart cavity by penetrating the myocardium direct or by penetrating a vein and being carried to the heart by the blood.* Here the foreign body is thrown around by the blood stream until it becomes attached to the wall by fibrin which later becomes organized. Apparently while the ball is free in the blood the patient may show many signs of cardiac irritability but these disappear when it becomes attached to the endocardium.

Missiles which gain admittance to the blood stream are sometimes described as being dangerous to life, because of the possibility of embolism either from thrombi formation or because the bullet itself acts as an embolus. Sudden death in one case was caused by a projectile entering the left ventricle and then being carried by the blood to block the ascending aorta. Cases also have been described where the bullet has entered the right side of the heart or one of the systemic veins, and was later driven into the pulmonary artery with rapidly fatal results (Klose⁷).

In recent years operative repair of heart wounds or cardiorrhaphy has been extensively developed. Rehn⁹ in 1896 performed the first successful operation of this kind on man, though previous unsuccessful attempts had been made by other surgeons and a suitable technic had also been worked out by animal experiments. Since then other surgeons have imitated Rehn with greater or less success. The war of 1914 to 1918, however, brought the procedure into almost common use and in place of merely suturing wounds in the heart wall, many operators have gone so far as to remove foreign bodies from the interior of the heart and on occasion to operate twice on the same heart. W. R. Smith¹⁰ believes that cardiorrhaphy has

* The editor has offered an additional curious example of survival with a bullet in the heart. On examining the heart of an apparently normal moose that had just been shot, a mushroomed rifle bullet of larger caliber than he was using was found free in the cavity of the right ventricle. Presumably the animal had survived a previous wound, in which the bullet had entered a large vein and been swept into the right side of the heart, where it acted for an indefinite period as a ball thrombus. Its rougher edges were smoothed off with fibrinous deposits. No portal of entry was found on the body or after careful examination of the excised heart.

markedly decreased the mortality of heart wounds; he estimates that probably 1 in 10 recover under expectant treatment, while 1 out of 2 cases get well when the operation is performed.

The 3 cases presented here are some that came to autopsy in the routine work of the Medical Examiner's Office of New York City. They demonstrate very strikingly the characteristics of the kind of bullet wounds of the heart that allows the patient to survive several days or longer.

Case Reports. CASE I. T. H., aged forty-one years, a strong, well developed, white man was shot three times in the back. About fifty minutes afterward, the ambulance took him to the hospital, where he was admitted in a state of shock, but conscious and rational. He showed considerable abdominal discomfort, his skin was pale and his breathing was shallow and rapid. Physical examination then disclosed three bullet wounds of entrance in the back, and the presence of a paralysis and a loss of sensation in that part of the body below the sixth dorsal vertebra.

He was operated on that same day under local anesthesia with the result that one bullet was removed from the left axilla and another, which had injured the spinal cord, was removed from the dorsal region of the spine by a laminectomy of the sixth and seventh dorsal vertebrae.

The patient survived the injury seven days with no improvement of his paraplegia and no alleviation of his abdominal distress, which was so acute that daily gastric lavage was necessary. During his entire illness he had a daily temperature of 99 to 101° F., accompanied by rapid pulse and respirations.

Autopsy was performed about thirty hours after death. The body was that of a large well developed adult male about 5 feet 10 inches in height. His skin had an icteric tinge; there was also a superficial bed sore in the sacral region. Bullet hole No. 1 was situated in the mid-thoracic region near the spine, not far from the laminectomy incision through which the bullet had been removed at operation. Bullet hole No. 2 was found alongside of the left axilla near another operative incision. Bullet wound No. 3 was located in the lower part of the left chest posteriorly at the level of the tenth interspace, $4\frac{1}{2}$ inches to the left of the spine.

On section, it was discovered that the bullet, 32 caliber lead, which made wound No. 3, passed through the left chest upward, forward, and to the right, fracturing the left eighth rib in the axillary region, perforating the left lung and the pericardium, wounding the heart and finally lodging in the upper lobe of the right lung. Both lungs showed an extensive pneumonic consolidation; the right lung was adherent to the chest wall. The left pleural cavity, however, contained 950 cc of dark fluid blood presumably due to the bullet wound of the left lung.

The pericardial cavity was of normal size and contained neither blood nor fluid. The pericardial wounds seemed to be healed. The muscle was moderately contracted but otherwise natural. Valves, aorta and coronary arteries showed nothing unusual. The heart wound was seen to be a small bluish red tunnel of the left ventricle $1\frac{1}{2}$ inches in length and about $\frac{3}{8}$ of an inch in diameter. The bullet had entered the muscle of the left ventricle near the left border and traveling forward and upward had emerged from the myocardium of the right ventricle near the septum. The cavity of the heart had not been entered nor had any important vessel been injured by the bullet.

CASE II.—H. R., aged twenty-three years, during a quarrel was shot once in the left chest anteriorly. He immediately lost consciousness but recovered rapidly. Shortly after this he was admitted to the hospital ward, displaying signs of severe shock. Examination disclosed a bullet hole in the left chest, situated about the level of a line drawn between the nipples and between the left nipple and the sternum. There was no wound of exit. Subsequent roentgen-ray examination located the bullet in the spinal column about the level of the seventh dorsal vertebra.

From the very start indications were not lacking that the spinal cord was injured at the level of the seventh dorsal spine, as sensation was disturbed and the muscles were paralyzed below that point, and incontinence of urine and feces was present. Three days after the injury, bedsores developed in the gluteal regions. The neck was rigid and the spinal fluid acquired by lumbar puncture contained blood cells. The blood count showed 19,000 white cells of which 86 per cent were polymorphonuclear leukocytes. The urine merely showed a few hyalin casts, a few white cells and a trace of albumin. There were also signs of fluid in the right chest.

The patient survived the injury eight days, with a consistently high temperature of 103° F., but showing a normal pulse and respiration rate until just before his death. Then he suddenly became markedly dyspneic and cyanotic, and died in the course of several minutes.

Autopsy was performed about fifteen hours after death. The body was that of a well developed young adult male, aged twenty-three years, 5 feet 8 inches tall, weighing 142 pounds. There were numerous bedsores over the sacrum, buttocks and heels.

There was a bullet wound of entrance on the front of the left chest, very small, about $\frac{2}{16}$ inches in diameter, located 2 inches to right of the left nipple and slightly above its level. The bullet then penetrated through the fourth left costal cartilage; perforated the pericardium, heart, thoracic aorta, finally entering the thoracic spine. The bullet, a 25 caliber yellow metal jacketed bullet, was found in the spinal cord at the level of the seventh dorsal segment.

The renal pelves and the bladder showed a definite inflammation of the mucous membrane as the result of this spinal injury.

There was an enormous hemorrhage in the posterior mediastinum which projected as a huge retroperitoneal hematoma into the right pleural cavity. The pleura here had been split and the right pleural cavity contained a large quantity of blood and blood clot so that the right lung was forced over toward the left. The left lung was edematous and adherent to the chest wall by easily detached fibrinous adhesions. Neither lung was wounded by the bullet.

A pericardial perforation was found. The pericardium contained about 250 cc of blood, which was from a recent rupture, as the serous surface was not covered by any fibrinous deposit. The heart was normal in size and contracted, showing a bullet wound through the anterior surface of the right ventricle just below the ring, with perforations of the pulmonary artery, one of the pulmonary cusps, the left auricle and the thoracic aorta. The source of the pericardial hemorrhage was a recent separation of the edges of the right ventricle wound, presumably because of some sudden rise of intracardiac pressure, which the newly formed granulation tissue was unable to sustain. Sudden death therefore resulted from the rise in pericardial tension, due to the hemorrhage into the pericardial sac from the small recent perforation on the anterior surface of the right ventricle. The other in and out wounds of the auricular septum and of the left auricle were closed.

CASE III.—E. W., a young colored man, was found in a cellar unconscious and smelling strongly of alcohol. He was removed to a hospital and died there three days later, never having regained consciousness.

Autopsy showed a young colored male, aged twenty-two years, 5 feet 11 inches tall, weighing 161 pounds. Death was found to be due to a fractured skull, a lacerated brain and an extensive bronchopneumonia, secondary to the head injury. During the course of the autopsy, however, it was discovered that the deceased had evidence of an old bullet wound of the heart and the right lung probably of several years duration.

Two circular scars on the inside and outside of the biceps area of the right arm, each about $\frac{1}{2}$ inch in diameter, a similar scar on the right chest immediately over an old fracture of the seventh rib, a cord-like scar of the lower lobe of the right lung, and finally the heart lesion itself indicated clearly enough the course of this old bullet wound.

The missile had evidently entered the pericardium on the right side, but at autopsy there was no trace of such a wound. Over the most dependant portion of the right auricle was a circular fibrous scar $\frac{3}{8}$ inch in diameter, which occupied the entire thickness of the auricle wall, for it was visible on the epicardial and the endocardial

surfaces. This was evidently the point where the bullet entered the heart, penetrating about $\frac{3}{4}$ inch, to lodge finally in the muscle of the right ventricle, just below the ring and just under the epicardium where it was plainly visible. (See Fig. 1.) The bullet, 38 caliber lead, was enclosed in a thick fibrous capsule.



Photograph of the heart in Case III showing the encapsulated bullet.

There was no reason to believe that the deceased suffered any untoward symptoms because of its presence in his myocardium, where it had obviously been for a very long time. Subsequent investigation failed to establish any reliable history of the old shooting, but it was suspected that the deceased was identical with a certain negro who had been shot three years before. Positive identification was impossible because of the fondness of the dead man for aliases.

Discussion. The three cases presented here are of value in that they suggest conditions under which healing can take place in the heart wall. In Case I, a 32 caliber bullet without penetrating the heart cavity cut a tunnel in a segment of the heart muscle that was not unduly vascular. There was practically no hemorrhage into

the pericardial cavity and death seemed to be due to the spinal cord lesion and the lobar pneumonia. In Case II the heart and aorta were perforated by a small 25 caliber bullet in such a manner that bleeding was slight at the start, the patient experiencing no trouble from his cardiac injury until eight days afterward when the edges of the wound were suddenly forced apart and death resulted from the sudden hemorrhage into the pericardium. In Case III, the remarkable feature was the encapsulation of the bullet in the right ventricle with healed scars of the right auricle and the right lung, demonstrating the manner in which the bullet had reached its final resting place many years before. Death in this case was due to a recent injury which had no connection with the old bullet wound. In all three cases the bullets left wounds of such a nature in the heart that the primary complications were avoided and conditions were favorable for the process of repair.

These cases are rather unique in comparison with the other bullet wounds of the heart that have come under the observation of the Medical Examiner's office, most of which die very rapidly after the shooting. Occasionally a cardiac wound is found in a person living a few hours to two days after the injury, such as when the accompanying pericardial wound drains the blood into the pleural cavity and prevents a rapidly fatal increase of intra-pericardial pressure. It is rare however to find bullet wounds of the heart that allow any longer survival and exceedingly rare to find one that undergoes spontaneous cure, as in Case III.

It is probably true that most of the previous statistics concerning the mortality of these injuries err somewhat on the side of optimism. Immediately fatal cases are rarely published and are thus overlooked. In addition, many chest wounds that recover without operation are often erroneously diagnosed as cardiac wounds by mere clinical observation, which in itself alone cannot determine the actual state of affairs inside the chest with any degree of certainty. Consequently to compile statistics under such conditions may be misleading and give rise to erroneous interpretations.

This does not diminish the value of the fact, however, that some bullet wounds of the heart do tend to undergo spontaneous healing and that others may be amenable to a suitable operation, a knowledge which is not only of importance to surgeons but to practitioners of forensic medicine. Not infrequently vital points of evidence in homicide cases can be made clear only by appreciating the fact that a cardiac wound need not necessarily kill outright and that the patient can under suitable circumstances survive the shooting for a considerable length of time.

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HEART BLOCK OF UNUSUAL ETIOLOGY.

By NORMAN E. CLARKE, M.S., M.D.,

AND

F. JANNEY SMITH, A.B., M.D.,

DETROIT.

(From the Department of Internal Medicine, Henry Ford Hospital, Detroit, Mich.)

THE occurrence of heart block is now rarely of sufficient interest to occasion comment. Its presence invariably means partial or complete destruction of the auriculoventricular pathway of conduction, provided toxic causes, such as digitalis, are excluded. It occurs usually in elderly individuals whose hearts show advanced myocardial degeneration and is in most instances a permanent condition.

We have recently observed two patients suffering from this disturbance, in whom the condition arose from a very unusual etiology. The association of heart block with gumma of the septum is exceptional. In a recent paper by Major¹ he was able to find but twelve such cases reported up to 1922.

Case Reports. CASE I.—A housewife, aged thirty-five years, entered the Henry Ford Hospital on April 13, 1924, complaining of severe dyspnea and precordial pain. During the preceding three years she had suffered from slight fainting attacks which occurred at irregular intervals. She always was aware of the approach of one of these attacks by everything becoming blurred,

breathing dyspnea and the necessity for her to sit down in order to avoid falling. Complete consciousness was never lost, but there was inability to move or talk during the attack. A year previously there had appeared in her left arm and shoulder and over the precordium momentary, fleeting pains of great severity. These pains were not associated with fear of death or induced by exercise. In spite of these symptoms her general health had remained fairly good, and she had been able to continue with her housework until November, 1923. She had partaken of an unusually heavy meal, when suddenly there occurred a severe pain about her heart and she lapsed into unconsciousness which lasted several minutes. From then on her dyspnea was pronounced, and within a short time edema appeared in the extremities, which symptoms steadily increased in severity and extent. The most striking feature at this time was her recognition of the fact that her heart rate had become very slow. During the three weeks previous to her admission to the hospital there had been extreme edema, ascites and orthopnea.

Her past history was essentially negative.

Physical examination showed a short, obese, young woman. The pupillary reaction to light and the tendon reflexes were prompt and normal. There was marked dyspnea and slight cyanosis. The veins of the neck were engorged, and a systolic pulsation could be felt in the suprasternal notch. The apex impulse was visible in the fifth space, 11 cm. from the midsternal line. The retrosternal dulness was increased, and tubular breath sounds were audible in this area. The heart rate was 48, the rhythm being slow and regular and the first sound at the apex muffled. The pulmonary second sound was very accentuated and distinctly reduplicated. At the apex and base there was a rough systolic murmur and a blowing diastolic murmur was heard along the left sternal border, the latter transmitted into the great vessels of the neck. Blood pressure was 190 systolic and 70 diastolic. There was congestion of both lung bases and extreme edema of both extremities. The blood Wassermann test was 4+.

During her brief stay in the hospital she had rapidly increasing decompensation. A few days before her death thrombosis of the left brachial and internal jugular vein occurred, with the production of local heat, tenderness, swelling, pain and intense cyanosis of the left arm. Death came with sudden increase in the dyspnea, intense cyanosis and collapse.

The initial electrocardiographic tracing made immediately after admission is shown in Fig. 1. The complexes were of low voltage with a *Q-R-S* interval of 0.12 to 0.16 of a second. There were notched and splintered *R* and *S* waves, flat *T* waves in Lead I, and inverted *T* waves in Lead II. The curve likewise showed complete heart block. The curve obviously showed severe myo-

cardial damage with destruction or blocking of the auricular ventricular pathway. The impulses appeared to arise in the left branch of the His bundle below the area of destruction. The later curves continued to show similar findings.

Report of Necropsy (Dr. Hartman): The heart was enlarged, weighing 550 gm. The wall of the right coronary artery was thickened, the lumen being partially occluded. The intima of the aorta showed numerous puckered, wrinkled thickenings with but few areas that were not so involved. There were no areas of calcification. The ascending portion of the aorta showed the most pronounced changes, but these pathological areas were present to a less degree in the larger branches. The aortic wall was thickened, and there were yellowish streaks of necrotic tissue between the media and the intima.

On opening the heart the chambers appeared dilated; the walls were thinner than normal. None of the valve leaflets were thickened, nor did they show any unusual changes. The ventricular septum showed a mass which bulged outward into both ventricles. This mass involved the auriculoventricular node and extended downward toward the apex for a distance of 6 cm., leaving only the apical half of the septum uninvolved. This new septal tissue was firmer and more resistant than normal, and in a section cut between the sinuses of Valsalva and downward toward the apex a change was noted from heart muscle to firm tough yellowish-gray tissue. The two endocardial surfaces were unaltered. The mass showed areas of yellowish necrotic material alternating with the grayish fibrous strands. The microscopical sections taken from the interventricular septum through the area of softening showed the muscle to be largely replaced by fibrous connective tissue, and the little muscle that remained was infiltrated here and there by round and wandering cells. In the immediate vicinity of the caseous area there was an intense infiltration by round and wandering and plasma cells. The area of destruction shaded gradually into the surrounding fibrous tissue and muscle, and about it was a zone of intense infiltration gradually changing from cells which stained well to those which stained a homogeneous dirty blue color with fragmented nuclei scattered throughout. Stains for spirochetes were made after the method of Warthin and Starry, and showed an occasional *Treponema pallidum*, identified by its size and short curves. Further sections through different areas of the interventricular septum were examined. These showed larger and smaller areas of round-cell and plasma-cell infiltration and areas of homogeneous dirty blue staining tissue much as previously described.

Our second patient presented numerous points of interest. The duration of his heart condition, the presence of a possibly associated gall-bladder infection, and ultimate recovery after the

operative removal of the abdominal lesion, constitute an experience which is not common among patients classified as heart cases.

CASE II.—This man, aged thirty-five years, first came under observation in our out-patient department in December, 1922. He complained of frequent colds, headaches, spells of weakness and occasional night sweats, with a slight daily rise in temperature. He had had typhoid fever several years previously and his general health had not been up to par since that time. The heart showed regular rhythm, a rate of 80 and sounds of good quality. There were no cardiac murmurs. The blood pressure was 100 systolic and 58 diastolic. Repeated physical examinations of the chest, together with roentgen rays, ruled out as far as possible any probability of pulmonary tuberculosis. He had definite involvement of the maxillary sinuses with chronically infected tonsils. A complete gastrointestinal examination revealed evidence which strongly suggested disease of the gall bladder.

In May, 1923, his heart was again examined with apparently normal findings. His spells of weakness and headaches still continued. From this time until March, 1924, he was under treatment for his constipation and chronic cholecystitis.

In March, 1924, he came to the hospital suffering from acute heart failure. He stated that ten days previously, while returning from lunch, he had climbed some stairs with comparative comfort. When he reached the top landing he saw black spots before his eyes and he suffered a feeling of faintness. On attempting to push forward he became very dyspneic, had a sense of suffocation, and it was necessary for him to sit down and rest. During the afternoon he had a similar attack of suffocation and a feeling of pounding in the region of his heart. These attacks had occurred daily up to his admission to the hospital. On a previous day, while walking a distance of about one mile, he had suffered frequent attacks which necessitated staggering to a tree or other support until he could regain his breath and balance. He described the feeling in his head as of "something rushing up into my skull and dilating my brain."

Examination. He was seen immediately after entering the out-patient department by one of us (N. E. C.). Heart failure was present with extreme cyanosis, dyspnea, moderate orthopnea and slight edema of the extremities. The heart rhythm at that time was absolutely irregular. While under examination the patient informed us that the extreme palpitation had suddenly stopped. He was sent to the "heart station" and an electrocardiogram was taken (Fig. 2). During his stay in the hospital he showed a slight elevation of temperature every three or four days. Fluoroscopic examination of the chest showed the heart to be slightly enlarged with slight prominence in the left auricular region.

An examination made after many days' rest in the hospital showed the following findings: There was palpable enlargement of the postcervical glands and moderate cyanosis of the lips. The maximum apex impulse was in the sixth interspace 9 cm. from the midsternal line inside the nipple line. The heart's rate was 80. The rhythm was regular with occasionally what appeared to be dropped beats. The sounds at the apex were only fair and rather distant. The second aortic sound was unusually accented, hollow and rather bell-like. The peripheral arteries were not palpable. The blood pressure was 105 systolic and 65 diastolic. The lungs were clear. The blood Wassermann on repeated examinations was always negative, and the spinal fluid was normal in all tests. He felt definite tenderness over McBurney's and Morris's point, but none over the gall-bladder region. There was no jaundice.

He remained in the hospital at absolute rest for about ten days, and when discharged had recovered from his acute symptoms. At this time he was advised to have an operation for the removal of his infected gall bladder.

On May 5, 1924, he was operated upon, and the appendix and gall bladder were removed. Pathological examination, by Dr. Hartman, showed the usual evidence of a chronic infection of these two organs.

He made an uneventful recovery from the operation. The constipation has persisted but the headaches have been almost completely relieved, and the heart has been so improved that at present he has none of his previous cardiac symptoms. He is symptomatically cured and is again able to carry on his daily work without difficulty. Since the operation he has gained 20 pounds in weight.

Electrocardiographic Examination. The first electrocardiogram (Fig. 2), taken in March, 1924, showed partial heart block with a $P-R$ interval of about 0.34 seconds and large P waves in Leads II and III, probably due to auricular engorgement.

On April 1, 1924, the electrocardiogram (Fig. 3) showed complete $A-V$ dissociation, with a ventricular rate of 58 and an auricular rate of 112. The P waves were not as prominent as they had been in the previous tracing. At this time the patient was exercised, but this had no effect whatever on the $P-R$ interval, but did increase the ventricular rate, causing a frequent summation of the P and T waves. The administration of amyl nitrite caused results similar to exercise. While the patient was undergoing examination he suffered from attacks characterized by a sudden staring expression, falling backward of his head, slumping of his body and momentary loss of consciousness. These periods were synchronously registered on the electrocardiogram as dropped ventricular beats, auricular impulses maintaining their regular rate and sequence. Atropin was administered intravenously in a $\frac{1}{30}$ -grain dose, resulting in



FIG. 1.—Case I.—Initial tracing taken at the time of admission showing complete heart block.

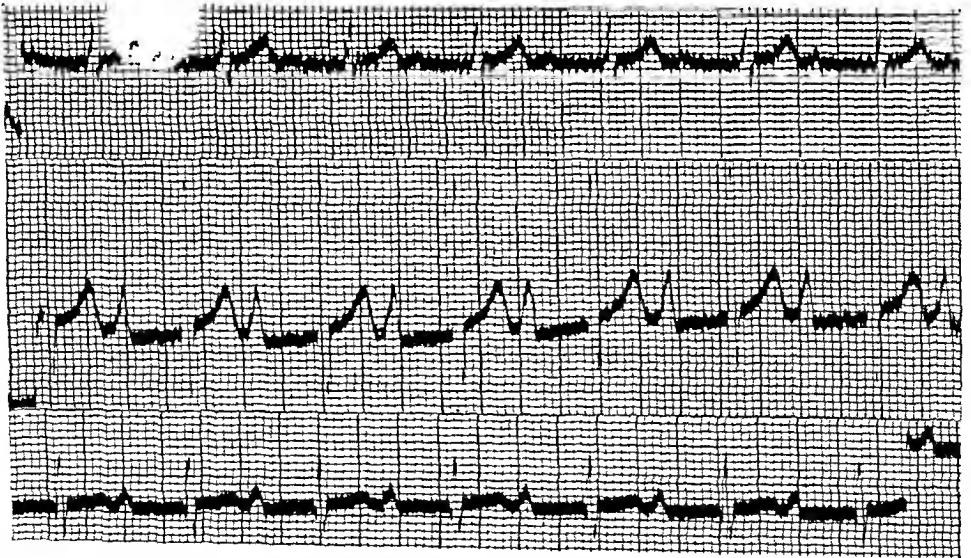


FIG. 2.—Case II. Initial tracing showing large *P* waves and partial heart block.



FIG. 3.—Case II. Tracing taken one month after onset of symptoms and showing complete auriculoventricular dissociation.

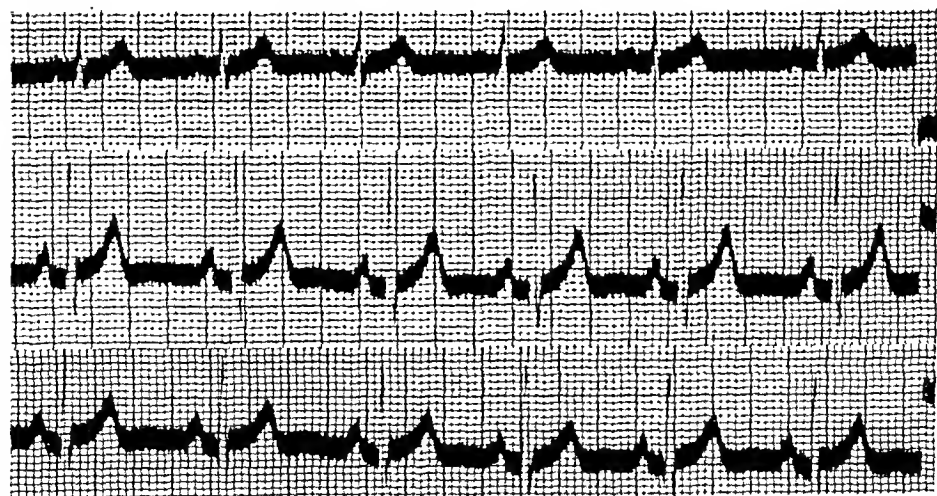


FIG. 4.—Case II. Normal tracing taken after cholecystectomy had been performed.

changes closely resembling those noted by exercise and amyl nitrite, namely, increase in heart rate with no tendency to return to sinus rhythm.

On April 24 the electrocardiogram showed a *P-R* interval of 0.48 second, the *P* wave following immediately after the *S* or *R* wave of the ventricular complex.

The patient had been given potassium iodide for a rather long period, and on May 2 the electrocardiogram showed a *P-R* interval of only 0.2 second.

On May 5 a tracing taken ten minutes after operation showed a *P-R* interval of 0.16 to 0.18 second.

From May 1, 1924, to January, 1925, many electrocardiographical tracings have been taken, all showing normal form (Fig. 4) with no suggestion of the previously noted abnormalities.

Comment. The patient with cardiac gumma presented the usual clinical picture of syphilis of the cardiovascular system, namely, a sudden and unexpected onset with a progressive downward course. We can only surmise that the initiating of her serious difficulty by an apparent Stokes-Adams attack might have also marked the sudden onset of her complete block. She had no similar attacks afterward. The diagnosis of gumma of the septum as a cause for the bundle destruction is conclusively proved by the demonstration in it of the *Spirocheta pallida*.

The second individual's entire story and progress was unusual. He likewise entered in a state of acute heart failure which was relatively sudden and unexpected in its onset. His heart showed complete auriculoventricular dissociation during the course of our observation, but he progressed to a complete symptomatic recovery with his heart resuming and maintaining normal sinus rhythm.

One might speculate on the relationship between the removal of the infected gall bladder, with the simultaneous recovery and maintenance of normal cardiac mechanism. The "cholecystitic heart" is a well-recognized condition, causing arrhythmia, tachycardia, bradycardia, precordial pain and distress, or even attacks simulating the picture known as angina pectoris. The question here is whether the infected gall bladder caused myocardial changes or strain which was relieved by its removal. This association of myocardial changes and gall-bladder infection has been discussed by Babcock,³ who has reported several cases in which he attributed myocardial weakness to biliary tract infection.

It is too early to say that this patient has made a permanent recovery. The auriculoventricular bundle having a large reserve conduction capacity may function without showing electrocardiographical changes when only a few strands remain. Under such conditions a slight circulatory change or vagus influence will cause block. This condition of partial-bundle destruction may be present

in this man, and the removal of the infected gall bladder by relieving a strain or a toxic effect on the heart might have been sufficient to raise the conduction threshold back to apparently normal function. The potassium iodide which was administered must also be considered in viewing the possible factors that caused the return to normal rhythm and conduction.

The duration of the heart block in this man appears to preclude any possibility of vagus influence being a factor.

Summary. A case of heart block due to gumma of the ventricular septum has been reported.

The diagnosis of gumma has been conclusively proved by the demonstration of the *Spirocheta pallida* in the ventricular tissues.

The possibility of gall bladder infection as a primary or accessory cause of heart block has been discussed.

A case illustrating the above possibility has been presented in which the heart regained and has maintained normal sinus rhythm since the removal of the infected gall bladder.

We wish to acknowledge our indebtedness to Dr. Frank Hartman for the pathological reports.

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OBSTRUCTIVE JAUNDICE.*

By E. STARR JUDD, M.D.,

AND

VERNE G. BURDEN, M.D.,

DIVISION OF SURGERY, MAYO CLINIC, ROCHESTER, MINNESOTA.

WITHIN the last few years, experimental research in the physiology of the biliary apparatus has materially increased our understanding of the basic principles involved in clinical disease of this system. There has been, we believe, a corresponding improvement in diagnosis and treatment. A greater part of the experimental work has been devoted to the consequences of mechanical disturbance of bile flow. While recognizing the great importance of this newer knowledge, we must therefore, be guarded in the application of experimental results in the animal to disease in man. Besides the differences in anatomic structure and physiology, there is the important

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factor of infection, which is the chief cause of disease in man, and is so difficult to reproduce at will in the experimental animal. It is true that the most serious diseases of the biliary tract are those in which the outstanding feature is biliary obstruction. Surgical mortality is practically confined to such cases. There has been, so far as we can determine, very little detailed clinical and laboratory investigation of patients with obstructive jaundice extending over the entire preoperative and postoperative course. The solution of these problems can only be attained by careful comparison of such clinical data with the already known experimental facts. With the idea of stimulating further investigation we report the following case.

A woman, aged forty-four years, came for examination November 29, 1921, because of attacks of abdominal pain. She had been married twenty-one years and had one child. Her present illness had begun one year before, with pain in the right side of the abdomen. A second attack occurred three months later and was followed by persistent soreness over the right side of the abdomen. There were two subsequent attacks about three weeks apart, and a physician was called to relieve the pain. There was no associated fever or vomiting, no jaundice or other symptoms except marked constipation.

The patient was 5 feet, 6 inches high, and weighed 118 pounds. The systolic blood pressure was 144, the diastolic 96. She appeared to be in good health. Abdominal examination was negative except that the right kidney was palpable and mobile. The urine was normal. The hemoglobin was 70 per cent, the leukocytes numbered 8,600. The phenolsulphonephthalein test showed a return of 70 per cent in two hours. Roentgen-ray examinations of the chest, kidneys, ureters, bladder and colon were negative. Electrocardiograms revealed a sinus tachycardia rate of 100. The diagnosis was made of chronic appendicitis, probably associated with cholecystitis, and operation was advised.

December, 9, operation was performed through the upper right rectus incision. The gall bladder was a reddish plum color and filled with stones. It was constricted at the middle, apparently by fibrous tissue. The common duct appeared normal, and stones could not be palpated. The stomach, duodenum, and uterus and adnexa were normal. The right kidney was located normally. The liver was not enlarged but was markedly prolapsed, the lower edge extending below the level of the umbilicus. The gall bladder and appendix were removed and the wound closed without drainage.

The pathologist reported subacute cholecystitis and a contraction in the middle of the gall bladder, and in this contracted portion an adenocarcinoma and squamous-cell epithelioma, grade 2, chole-

lithiasis (multiple stones, the largest 1.5 cm. in diameter), and chronic catarrhal appendicitis (Figs. 1 and 2).

The wound healed by primary union. The patient was dismissed from the hospital on the eleventh day, and returned to her home on the seventeenth day. She returned for examination, September 22, 1924, two years and nine months after the operation. She had been in excellent health until two months before when she had a peculiar uncomfortable sensation high in the epigastrium with a feeling of "drawing." There was no pain. Two weeks later jaundice appeared which became progressively deeper. There was severe pruritus. The urine was dark and the stools clay colored.

The patient now weighed 114 pounds. The systolic blood pressure was 134, the diastolic 88. Jaundice was marked. The liver margin extended below the umbilicus and the surface appeared to be irregular. Urinalysis disclosed a trace of albumin, a large amount of bile, a few hyalin and granular casts, and an occasional pus and red blood cell. The hemoglobin was 67 per cent, the erythrocytes numbered 4,130,000, and the leukocytes 5200. The coagulation time was seven and a half minutes (September 24). Roentgen-ray examinations of the chest and the stomach were negative. Examinations of the stool showed an excess of fat. The patient was sent into the hospital for observation.

September 26, 1924, a test of liver function revealed dye retention, grade 4; serum bilirubin 21.1 mg. for each 100 cc; blood creatinin 1.3 mg. for each 100 cc; and blood uric acid 2.3 mg. for each 100 cc. September 30, the coagulation time was nine and a half minutes, calcium time nine minutes, bleeding time three and a half minutes. These tests were made after the patient had received 4 intravenous injections of 5 cc of 10 per cent calcium chloride. During this time the jaundice had become much deeper.

In view of the previous malignant condition in the gall bladder and the recent onset of painless jaundice it now seemed that a malignant lesion must be causing biliary obstruction. However, the interval of two years and nine months since the previous operation seemed to favor the possibility of a benign stricture of the common duct. The patient was again given a course of calcium chloride intravenously. Fluid intake was increased and quantities of glucose were given by mouth. October 18, biliary obstruction with constant progressive jaundice had existed for eleven weeks. Calcium chloride had been used to improve the coagulation time of the blood. The patient's general condition was excellent. The calcium time was ten minutes and fifteen seconds; the coagulation time eleven minutes. The serum bilirubin was 35.4 mg. for each 100 cc. The bleeding time was three minutes. The salivary urea index was 38 (blood urea 20 mg.).

The risk of operation and the slight hope of cure were explained to the patient and her husband, but they were both anxious to have



FIG. 1.—Area in gall bladder showing squamous cell epithelioma. ($\times 200$.)



FIG. 2.—Area in gall bladder showing small cell adenocarcinoma. ($\times 400$.)



something done. Therefore, October 20, operation was performed under ether anesthesia. The liver appeared as usual in cases of biliary obstruction. It was enlarged, with rounded edges, mottled, and a dark slate color. Its surface was smooth and uniform. By following the gall bladder notch and keeping close to the liver in dissecting through a mass of scar tissue, the hilus was located. A careful search was made for the common duct but it could not be found. This area was a dense mass of fibrous tissue. Finally a small "bud" was found at the margin of the liver. This was opened and a gush of clear watery fluid, the so called white bile, appeared. A probe was inserted with difficulty along the duct for a short distance into the liver. A passage way distally toward the duodenum could not be found. A small rubber catheter was fastened into this duct which was probably a branch of the main hepatic duct. Several pieces of tissue were excised from the region of the hilus of the liver and examined microscopically; inflammation, marked fibrosis and duct regeneration were found. Two Penrose drains were placed down to the site of operation. The superior surface of the liver, which was widely exposed, was then punctured in many places with a large needle and each time there was a gush of white bile. An ordinary white sponge was placed on the surface of the liver and allowed to remain for drainage. The wound was closed in layers around the drains.

The patient withstood the operation very well, but a transfusion of 500 cc of blood by the citrate method was given as a prophylactic measure.

October 25, bile drainage first appeared.

October 26, bloody drainage appeared; the temperature was 102°, the pulse rate 100.

October 27, the blood urea was 110 mg. for each 100 cc, the creatinin was 2.3 mg. for each 100 cc; the coagulation time eleven minutes, the calcium time ten minutes and fifteen seconds, and the serum bilirubin was 28.6 mg. for each 100 cc.

October 28, the patient had received 3 injections of calcium chloride solution. The coagulation time was ten minutes and forty-five seconds, the calcium time eleven minutes and fifteen seconds.

November 3, the temperature was 100, and the pulse 110. There was considerable edema of the lower limbs, hyperpnea, and complaint of pain in the lower right chest. Examination of the lungs was negative. The drainage of bile varied. The patient was mentally clear and apparently doing well. The blood urea was 240 mg. for each 100 cc, and the creatinin 4.7 mg. for each 100 cc. The output of urine averaged more than 1300 cc daily.

November 5, the blood urea was 259 mg. for each 100 cc; carbon dioxide 20 volumes per cent; and chlorides 570 mg. for each 100 cc.

November 6, the blood urea was 252 mg. for each 100 cc; carbon dioxide 29 volumes per cent, and chlorides 568 mg. for each 100 cc.

November 7, the blood urca was 231 mg. for each 100 cc; carbon dioxide 22 volumes per cent, and chlorides 611 mg. for each 100 cc. Urinalysis revealed only a trace of albumin and a few pus cells. The leukocytes numbered 15,800, the hemoglobin was 40 per cent.

November 8, the blood urea was 215 mg. for each 100 cc; carbon dioxide 28 volumes per cent, and chlorides 571 mg. for each 100 cc. There was good drainage of bile.

November 10, the blood urea was 251 mg. for each 100 cc, and chlorides 637 mg. for each 100 cc.

November 11, the blood urca was 189 mg. for each 100 cc; carbon dioxide 32 volumes per cent, and chlorides 624 mg. for each 100 cc.

November 12, the blood urca was 144 mg. for each 100 cc; carbon dioxide 26 volumes per cent, and chlorides 619 mg. for each 100 cc.

November 13, the blood urca was 117 mg. for each 100 cc, and the chlorides 616 mg. for each 100 cc. The patient was given, intravenously, 1000 cc of 10 per cent glucose and 4 per cent sodium bicarbonate at 5.30 P.M., after which the blood urea was 253 mg. for each 100 cc; the carbon dioxide 24 volumes per cent; the chlorides 609 mg. for each 100 cc, and the serum bilirubin 4.2 mg. for each 100 cc. For several days there had been bile in the stools and diminishing jaundice. Removal of the gauze drain was started on the twelfth day and completed on the sixteenth. The Penrose and Robson drains had been removed.*

November 14, an intravenous injection of 500 cc of 10 per cent glucose and 4 per cent sodium bicarbonate was given. The urinalysis revealed a trace of albumin, bile, urobilin, no casts and an occasional pus cell.

November 15, an intravenous injection of 250 cc of 10 per cent glucose and 4 per cent sodium bicarbonate was given. The blood urea was 92 mg. for each 100 cc; carbon dioxide 56 volumes per cent, and chlorides 570 mg. for each 100 cc.

November 17, the blood urca was 70 mg. for each 100 cc; carbon dioxide 82 volumes per cent, and the chlorides 506 mg. for each 100 cc.

November 18, the blood urea was 49 mg. for each 100 cc; carbon dioxide 76 volumes per cent, and the chlorides 519 mg. for each 100 cc. The patient's general condition was so much improved that

* It may be noted that on November 3 and 5, the laboratory reports indicated a condition of renal insufficiency and acidosis. A solution of 375 cc of 4 per cent sodium bicarbonate and 20 per cent glucose was given intravenously. There was a responsive improvement in the acidosis, as shown by the increased carbon dioxide combining power of the blood. During the succeeding seven days glucose solution was given intravenously almost daily, sometimes in combination with sodium bicarbonate or sodium chloride. The only reaction occurred November 13. The patient's condition was markedly improved. It is of interest to contrast the daily laboratory reports of the relative values of blood urea, carbon dioxide, and chlorides with the findings in the acute toxemia of intestinal stasis. The blood urea was high, the blood chlorides were normal, and there was acidosis. With the toxemia of stasis the blood urea is high, the plasma chlorides are diminished and there is an increase in the alkali reserve.⁵

she was allowed to be up in a wheel chair. Bile drainage continued but the stools were natural in color. Her appetite was good; her only complaint was weakness.

November 20, the blood urea was 48 mg. for each 100 cc; carbon dioxide 65 volumes per cent, and the chlorides 540 mg. for each 100 cc.

November 21, the patient complained of pain in the right lower chest, which was worse on deep inspiration. The temperature was 101°. There was no drainage of bile to the outside for twenty-four hours.

November 22, the patient was much improved.

November 24, the blood urea was 36 mg. for each 100 cc; carbon dioxide 70 volumes per cent, and the chlorides 579 mg. for each 100 cc. The output of urine averaged about 1000 cc daily. There was free drainage of bile. The patient was walking with assistance. During convalescence the temperature remained around 99.5°, but several times took a sharp rise to 102°.

December 2, the blood urea was 23 mg. for each 100 cc; the carbon dioxide 52 volumes per cent, and chlorides 621 mg. for each 100 cc.

December 9, the patient was dismissed from the hospital. The stools were normal in color. The jaundice, judging from the appearance of the sclera, had entirely disappeared. The wound continued to drain a small quantity of bile and required a change of dressing daily. The entire right hypochondrium was filled by the liver which extended to the level of the umbilicus.

The patient was kept under observation at a convalescent home. While there she had several attacks of pain in the right hypochondrium which were promptly relieved by resumption of drainage from the biliary fistula. She gained in weight and strength and was allowed to go home January 6, 1925. At that time there was no trace of jaundice. A fistula was discharging bile but there was also bile in the stools.

Discussion. The value of the intravenous administration of calcium chloride in the preoperative preparation of jaundiced patients is well known. Walters has shown that by this method the prolonged coagulation time of the blood is brought within the limits of safety. Our practice is to give, on successive days, 3 intravenous injections of 5 cc of a 10 per cent solution of calcium chloride. If improvement is not satisfactory these injections are repeated after an interval of several days. There is no untoward effect on renal function following such dosage.¹ The patient seems to improve independently of the reduced coagulation time of the blood. This is borne out by the experimental results of King, Bigelow, and Pearce in cases of obstructive jaundice. They found an increase in the calcium content of the blood and kidneys and suggested that the calcium is bound to the bile pigments to neutralize their toxic effects, and is probably not available for the clotting of blood. There

is also a loss of calcium in the feces. The mobilization and expenditure of calcium probably occur at the expense of bone. It therefore seems probable that the administration of calcium to jaundiced patients not only improves the coagulation of the blood but helps to neutralize the toxic effects of bile in the blood. Although our patient had been deeply jaundiced for eleven weeks, there was no oozing of blood after the operation. Another point of interest in our case is that nearly three years after the operation there was no local evidence of recurrence of the malignant condition, either grossly or in microscopic sections removed from the region of the gall bladder. It is possible that in early carcinoma of the gall bladder, usually an accidental finding with gall stones, cholecystectomy will effect a cure, although this lesion provides some of the darkest pages in the dark chapters on carcinoma.

There are several features in our case that seem to defy explanation: The complete absence of a common duct. There had been an uncomplicated cholecystectomy for stones at which time the common duct appeared to be normal and was not opened. The wound which was closed without drainage healed by primary union and the patient was dismissed from the hospital on the eleventh day. She remained entirely well for more than two and a half years when painless jaundice developed. The process might have been an obliterative cholangitis analogous to a similar condition often seen in the appendix. We cannot explain the passage of bile into the intestine unless by a pocket connecting the bile duct with the duodenum. At the time of operation there was no passage way for the bile to the intestine, and none was made.

The liver in cases of obstructive jaundice has been the subject of much study. In the dog, where anatomic arrangement permits ducts draining separate portions to be occluded, it has been shown that obstruction of bile from a portion of the liver leads to complete parenchymal atrophy in that part. A very small part of the liver is sufficient to carry on the work of the whole.³ However, when the common duct is occluded the entire liver is affected, and the patient dies when demonstrable hepatic changes are only slight. Our case afforded a clinical example of the "white system" described by Rous and McMaster. When the stump of the hepatic duct was opened there was a gush of white bile under pressure. They give a more accurate description which fits this instance under the term *hydro-hepatosis*.⁴ In this condition, the intrahepatic bile ducts are distended with a thin colorless fluid which is devoid of bile salts or pigment, and which is a secretion of the ducts themselves.⁷ In many respects it is analogous to hydronephrosis. In this case and in many similar cases we have pierced the upper surface of the liver deeply in many places with a large needle. This is followed by free oozing of a thin colorless fluid from the puncture holes. A continu-

ous slow decompression of the liver results. The bleeding is not troublesome.

Glucose is of great value for these very sick and jaundiced patients. According to Mann it is almost a specific for hepatic insufficiency. It may be given intravenously in 10 per cent solution. Blood transfusion is also a helpful, although there has been no actual loss of blood.

While the liver has a wide margin of safety, its functional capacity cannot be estimated accurately in cases of obstructive jaundice. It is common knowledge that operation for relief of biliary obstruction is often followed by variable and uncertain events, particularly when the ducts contain white bile. In some cases there is good drainage of normal colored bile very soon after operation; in some, pigment may not appear for several days, or having once appeared will stop, and in others, bile fails to appear in spite of unobstructed drainage, and the patient dies from so called cholemia. Such events cannot be forecast at operation, and there is no fixed relation to the duration or degree of jaundice. The underlying factor is probably the functional capacity of the liver. Rous and McMaster have suggested that the rate of the disappearance of jaundice after relief from biliary obstruction might furnish an index of hepatic function. In our case the intrahepatic ducts were filled with white bile, and bile pigment did not appear in the drainage until the sixth day after operation. The serum bilirubin, which was 35.4 mg. for each 100 cc two days before operation, dropped to 28.6 on the eighth day after operation, and twenty-five days afterward it was 4.2 mg. for each 100 cc.

One of the chief symptoms of which jaundiced patients complain is an intolerable pruritus, which is a constant menace to rest. This symptom often precedes the definite appearance of jaundice. The ordinary methods of relief are futile. The most marked benefit we have seen has followed the use of diathermy, but the relief is temporary and is not so easily obtained by subsequent treatments. We noted, in many instances, that the pruritus completely and promptly disappeared following the establishment of free drainage of bile after biliary obstruction long before a reasonable time for the elimination of retained bile salts. That the itching is not caused by the increased bile pigment in the blood is demonstrated by the fact that many patients, when relieved from their obstruction, may nevertheless remain jaundiced for several weeks, but they do not have pruritus, and with hemolytic jaundice, itching does not occur.

Summary. A case of postoperative obstructive jaundice is reported. Significant laboratory studies were made of the blood before and after operation. There was no evidence of recurrence more than two and a half years after removal of a cancer of the gall bladder. A method is described of decompression of the liver by multiple needle punctures into the hepatic parenchyma.

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REVIEWS.

A TEXTBOOK OF PRACTICAL THERAPEUTICS. By HOBART AMORY HARE, B.Sc., M.D., LL.D., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College of Philadelphia; Physician to the Jefferson Medical College Hospital; one-time Clinical Professor of Diseases of Children in the University of Pennsylvania; one-time Commander, M.C., U.S.N.R.F. Nineteenth edition. Pp. 1061; 144 engravings and 8 plates. Philadelphia and New York: Lea & Febiger, 1925.

HARE'S *Practical Therapeutics* needs no eulogy and adverse criticism of it is almost impossible. It is a finished product and the profession's approval of it is evidenced by the nineteen editions. This last one particularly will make its appeal because of the numerous additions to the text. Among these may be mentioned sulpharsphenamin, insulin and the newer hypnotics. Even certain drugs, such as dial and medinal, which have not as yet been accepted by the Council on Pharmacy and Chemistry of the American Medical Association, are included. It is only fair perhaps, in spite of what has been said, to point out that some of the illustrations are somewhat antiquated and that there is an error on page 132 where it is stated that the spinal fluid should be withdrawn until the manometer shows the pressure to be about 30 mm. of "mercury."

T. M.

CHEMISTRY AND CHEMICAL URINALYSIS FOR NURSES. By HAROLD L. AMOSS, M.D. Third edition. Pp. 241. Philadelphia: Lea & Febiger, 1925. Price, \$2.25.

CHEMISTRY, as taught in schools of nursing, due to the limited time, must of necessity cover only a few general principles which may be applied to nursing. The writer has endeavored to adapt his book to the needs of the student nurse; however, the nursing references are not as numerous as might be desired. Throughout the text important words and statements are in italics and the divisions of each chapter are readily seen in bold black type. Each chapter is concluded by a brief summary which is concise and should serve as an excellent review. The text as a whole is interestingly written, the arrangement of subject material is good, and it should be an excellent text for the teacher of nurses or the student who wishes to continue her study of chemistry.

E. K.

THE ADVANCE OF ORTHOPEDIC SURGERY. By A. H. TUBBY, C.B., C.B.E., M.S. (LOND.), F.R.C.S. (ENG.), F.S.A. COL. R.A.M.C. (retired), and formerly Consulting Surgeon, Mediterranean and Egyptian Expeditionary Forces; Consulting Surgeon to the Westminster Royal National Orthopedic, Evelina and Christ's Hospitals; Member of the International Society of Surgery, of the Société Française de Chirurgie, of the Société de Chirurgie de Paris, and of the British Orthopedic Society; Corresponding Member of the American Orthopedic Association. Reprinted from the *Clinical Journal*. Pp. 144; 31 illustrations. London: H. K. Lewis & Co., Ltd., 1924.

THE author offers six articles written for *The Clinical Journal* and republished in book form which abstract the advances made in Orthopedic Surgery in the last twelve years. The roentgen-ray diagnosis of bone and joint conditions is covered most completely. The congenital and growth deformities are well described and well illustrated, and given in very practical form. The dangers of static and postural conditions are well emphasized. The infantile and spastic paralysis with discussion of etiological diagnosis and treatment are most comprehensively covered. The problem of the care and cure of cripples in large communities is thoroughly discussed.

D. W.

ON THE BREAST. By DUNCAN C. L. FITZWILLIAMS, St. Mary's Hospital, Paddington. Pp. 440; numerous illustrations. St. Louis: C. V. Mosby Company, 1925.

IN this, the American edition of the English work by the above-mentioned author, attempt has been made to furnish the surgeon, the student and the general practitioner with a condensed and adequate detailed account of the diseases of the breast and the methods of treatment. It is well stated that the majority of the works on breast are either too exhaustive for a busy man to wade through or too elementary to be of any use in connection with a case needing reference. The author furnishes the reader with clear-cut clinical pictures that are of sufficient fulness of description to be of reference value. Scattered throughout the text are numerous case histories and references which tend to fix in the reader's mind the essential embryologic, pathologic and anatomic features concerned with the condition under discussion. The book is profusely illustrated by pen and ink drawings, the majority of which are original. My one criticism of the illustrations is that possibly a little too much emphasis is placed upon the monstrosities of pathology. The book can be well recommended for student perusal.

E. E.

PHYSICAL CHEMISTRY FOR STUDENTS OF MEDICINE. By ALEXANDER FINDLAY, M.A., D.Sc., F.I.C., Professor of Chemistry, University of Aberdeen. Pp. 227. London: Longmans, Green and Company, 1924.

PROFESSOR FINDLAY, a recognized authority in physical chemistry, has contributed an elementary work based on the course in medical physical chemistry as given at the University of Aberdeen. The theoretical treatment is expounded in the author's usual explicit style, and is well illustrated by examples selected from medical and biological literature. The rapid growth of this subject has probably precluded the introduction of some more recent applications, though as a guide to these advances, this book should be welcomed by teachers, investigators and clinicians alike. B. O.

GONORRHEA. By DAVID THOMSON, Honorary Pathologist and Director of the "Pickett-Thomson" Research Laboratory, St. Paul's Hospital, London. Pp. 519; 22 illustrations and 21 plates, 2 in colors. London: Henry Frowde, Hodder & Stoughton, 1923.

THE monograph under consideration is very comprehensive in its scope, dealing with every aspect of gonorrhea. The author has done much research in this field and the results of his investigations concerning the complement fixation test and vaccine therapy are given at length. The publishers can feel proud of the volume, as it is most attractive in appearance, contains beautiful photomicrographs and colored plates, and the many bibliographies in various parts of the work are of real value. The section devoted to the female organs is not as complete as the remainder of the book; for example, stricture of the female urethra is not mentioned and pelvic inflammatory disease is very superficially, and to American minds, very poorly presented. As monographs appeal most strongly to specialists, this volume should be of interest to the urologist, serologist and bacteriologist. F. B.

GYNECOLOGY WITH OBSTETRICS. By JOHN S. FAIRBAIRN, Obstetric Physician, St. Thomas's Hospital, London. Pp. 769; 129 illustrations and 5 plates. London: Oxford University Press, 1924.

THIS book is intended for students and is of sufficient scope to be of value to them. In the beginning of the book is a rather

interesting historical prologue, although it will probably appeal very little to the average student. In the treatment of the subjects announced this book goes into somewhat more detail than the average handbook or manual, although it does not compete with the standard large textbook. On the whole, the section on obstetrics is better presented than the part devoted to gynecology, and the omission of any reference to Rubin's tubal inflation test and Sampson's interesting work with "chocolate" cysts of the ovary can hardly escape the notice of an American reviewer. Some of the illustrations are very satisfactory, but many of them are simple line drawings. Aside from being useful as a student's handbook, it might be helpful as a quick reference to general practitioners.

F.B.

A LABORATORY MANUAL OF PHYSIOLOGICAL CHEMISTRY. By E. W. ROCKWOOD and P. R. ROCKWOOD, Department of Chemistry and Toxicology, University of Iowa and the Mayo Foundation. Fifth edition. Pp. 406; 43 illustrations. Philadelphia: F. A. Davis Company, 1924.

THIS volume is a very good laboratory textbook for a rather extensive course in physiological chemistry, designed especially for medical students. The material is up to date and arranged in a very systematic manner, beginning with the foodstuffs and ending with the excretion of the urine. The chapter on Acid-base Equilibrium is brief and somewhat incomplete, but probably sufficient for medical students. The methods for blood and urine constituents are well chosen, complete and comprehensive. The arrangement of the book is not as inviting as some similar manuals, but the experiments are in general better selected.

W. K.

OPERATIVE SURGERY. By J. SHELTON HORSLEY, M.D., F.A.C.S., St. Elizabeth's Hospital, Richmond, Va. Pp. 784; 666 illustrations. St. Louis: C. V. Mosby Company, 1925.

THE greatest change in the second edition of this book is in the addition of a chapter on The Principles of Operations for Malignant Growths, in which some of the recent views of cancer are stated and their bearings upon operation for the cure of malignant tumor is noted. Among the interesting new operations described in this edition are the following: The lymphaticostomy of Costain, the operation of Stookey for innervating paralyzed muscles, the pylorotomy of Finney, the pulmonary lobectomy of Graham, the valvotomy of Cutler for mitral stenosis, the operation for angina

pectoris, the chordotomy of Frazier and the intestinal resection of Kerr. The operations of Crile for partial lobectomy of the thyroid and for ligation of the superior thyroid arteries are fully described, as well as gastroenterostomy and gastrectomy. The book is nicely gotten up, well written, cleverly illustrated and represents the last word in operative surgery.

E. E.

DISEASES OF THE RECTUM. By MARTIN L. BODKIN, M.D., F.A.C.S. Pp. 487; 111 illustrations. New York: E. B. Treat & Co., 1925.

THIS, the second edition of the work, has added chapters on Irrigation of the Colon, Superficial Diseases of the Anal Region and Relation of the Intestinal Flora to the Simple Catarrhal Diseases of the Colon. The older material on operations and treatment of malignant diseases has received careful revision. A special chapter has been added on Perianal Diseases, and a great deal of attention given to the bacteriology causing the different types of intestinal mucosa diseases. Attention is further given to the relation of rectal diseases to gynecology. The book is at once a practical and comprehensive treatise on this very important subject. It is well illustrated by good illustrations, printed on excellent paper and written in an easy, pleasing style.

E. E.

MEDICINE. AN HISTORICAL OUTLINE. By M. G. SEELIG, M.D., Professor of Clinical Surgery in the Washington University School of Medicine. Pp. 207; 48 plates. Baltimore: Williams and Wilkins Company, 1925.

UNDERGRADUATE acquaintance with even the high lights of medical history is unfortunately becoming more or more imperfect in these days of crowded curricula, when the unfortunate student must not only have acquired certain premedical scientific requisites, but must also squeeze into his already inadequate four years the steadily increasing bulk of medical and borderline knowledge. Not only must the clinical and preclinical subjects be taught by the necessarily time consuming "laboratory method" of instruction; but new instrumental methods and new subjects such as biophysics and physical chemistry are constantly crowding for recognition. Small wonder then that such apparent unessentials as the past history of medical art, teeming as it is with foolish errors and superstition, is neglected. Let the dead bury its dead!

But is not perhaps medical education like Macbeth's "vaulting

ambition which overleaps itself and falls on the other?" Is not the present method in some ways impractical and inefficient? Surely complete ignorance on the part of the student, say, of the man, time and circumstances connected with the discovery of the tubercle bacillus, must handicap his ability to deal with tuberculosis, necessitate more time in teaching him its "practical" phases and leave him more defenseless against the propagator of future errors. As Charles Singer maintains and demonstrates in London, sensible lectures on medical history not only provide the hearers with a better perspective of their subject, but actually save curricular time by offering a common foundation and often preventing repetition.

Anyone sympathizing with this point of view will welcome Major Seelig's book. Presenting the high lights of medicine in a somewhat breezy and attractive manner, it is well calculated to "tempt the student to dip into medical history." With Garrison's well known history and our interesting *Annals of Medical History* easily available, there is little likelihood of the awakened interest being later frightened away from the subject by the bulk of ponderous authorities. The reviewer thoroughly agrees with the remarks of Dr. Garrison in the Foreword that "the lectures are fresh, informing, brief and to the point . . . while the author's racy idiom, the stimulus of his enthusiasm and his slant on various matters are his very own." The St. Louis schools of medicine are to be congratulated on having the originals of these lectures available for their senior students. May the example prove contagious!

E. K.

COSMETIC SURGERY—THE CORRECTION OF FEATURAL IMPERFECTIONS. By CHARLES CONRAD MILLER. Pp. 263; 141 illustrations. Philadelphia: F. A. Davis Company, 1924.

THE object of this book is to be a guide to the surgeon in the correction of cosmetic defects of the face. The author describes numerous operations for the correction of folds, tags and wrinkles about the eyes, for the lifting of the face, for altering the palpebral interval, for the correction of double chin, for the softening of nasolabial lines, for the eradication of seowl lines, the formation of dimples, and other similar procedures. When he says that "all operations described in the book—can therefore be performed in the office quite as well as in a hospital operating room" he is minimizing a branch of surgery which is technical and demands considerable ingenuity in its performance. While a few of the author's operations have something to commend them, such as that for partial stenosis of the nose or for the correction of outstanding ears, there is considerable doubt in the reviewer's mind as to the end results obtained from most of the procedures suggested. Among these

are the operation for double chin and that for the removal of nasal bumps. The majority of the operations are inadequately described, the illustrations are not anatomical and the author has included no photographs of end results of his own cases. The operations are made to appear too simple and the reviewer fears that the book may do actual harm in leading the inexperienced surgeon to attempt technically difficult procedures without forewarning as to the difficulties which he will encounter.

There is considerable question as to the ethics involved in performing operations of this type. The author realized the possibility of criticism when he said, "in the face of possible strictures from the best in the profession, the writer offers these pages to those who may be interested."

I. R.

HEREDITY IN NERVOUS AND MENTAL DISEASE. An investigation by The Association for Research in Nervous and Mental Disease. Pp. 332; 48 illustrations. New York: Paul B. Hoeber, Inc., 1925.

A MONOGRAPH consisting of a series of well-prepared articles on the various phases of heredity in nervous and mental disease. Five main subdivisions are considered: I. The role of the cell and the chromosomes and the significance of exogenous and endogenous factors in heredity. II. The parts of the central nervous system which tend to exhibit morbid recessive or dominant characters. III. Pathological aspects: in the nervous system, in the extra-neural systems and experimental degeneracy. IV. Heredity in the psychoses. V. Heredity in literature.

The book is well edited, the discussion is lively and serves to bring out the salient points, and the illustrations are excellent. Certain articles deserve more than passing mention: "The Modern and Technical Study of Heredity" by Charles L. Dana; "The Cellular Basis of Inheritance" by Charles W. Metz, with a discussion of 11 pages; "Experimental Production of Degeneracy" by Charles R. Stockard and Albert M. Barrett's contribution on "The Heredity and Familial Factors in the Development of the Psychoses."

N. W.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE.

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI.

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Studies on the Pathological Histology of Experimental Carbon Tetrachloride Poisoning.—The large number of patients, over 1,000,000, who have been treated for hookworm and other parasitic worms with carbon tetrachloride, testify to the value of this preparation as an anthelmintic. It is comparatively pleasant to take, or at least it is much less disagreeable than other anthelmintics and it has been found relatively safe. However, the fact that several deaths have occurred following the administration of CCl_4 led GARDNER and others (*Bull. Johns Hopkins Hosp.*, 1925, 36, 107), at the request of the International Health Board, to undertake a study of the toxicity, pharmacology and pathological changes that take place following its ingestion. For the purposes of the investigation 240 dogs were employed; chemically pure CCl_4 was secured; the drug was given by stomach tube, subcutaneously, intraperitoneally, by inhalation, by rectum and intravenously; and various size doses were given per kilo of body weight. The drug was also given in conjunction with cream and with alcohol. The authors accentuate in the report that the only lesion worthy of note produced by carbon tetrachloride is a central necrosis of the liver. This is observed as early as twelve hours after oral administration and may be produced by an oral dose of the drug equivalent to 0.5 cc per kilo of body weight. Healing of the liver lesion begins three to four days after the oral administration of the drug and is not completed in five weeks. In addition to the result that the authors stress in their paper, there are two or three other points upon which it is interesting to

speculate. They note that puppies are more susceptible to the drug than adult dogs and that rabbits are more susceptible than dogs, probably because there is no cathartic action from the drug in rabbits as there is in man and dog. Among the 12 puppies that were given equivalent dosage for weight, 6 died and of the 6 who died 3 had masses of dead roundworms in their small intestine. These latter results suggest the advisability of using the drug with extreme caution when administered to children, not only because the liver of the young seems to be more susceptible, but also because of the possibility that in children roundworms may be present which might cause a partial or incomplete obstruction of the lumen of the intestine when killed by the action of the drug and a consequent slower elimination than when peristaltic action is unimpeded. Such a sequence of events apparently occurred in a fatal case recently seen following administration of CCl_4 and as yet unreported. The masses of dead worms in the intestine of the child were sufficiently obstructive apparently to cause a retention of the drug which killed the child by its action on the liver cells, as confirmed by autopsy a few hours after ingestion. The studies of the authors would make it seem proper to utter a word of caution to those who would administer CCl_4 to children and more particularly to children who might have an infestation of the large worm parasites as well as hookworms.

Contributions to the Pathology of Experimental Virus Encephalitis.
III Varieties and Properties of the Herpes Virus.—SIMON FLEXNER and H. L. AMOSS (*Jour. Exper. Med.*, 1925, 41, 357) in the third paper of the series dealing with experimental virus encephalitis, recount their experiences with, and studies of, some strains of the herpes virus which are much less likely to produce encephalitis in the rabbit than the two highly virulent strains, previously reported upon. With these mild strains the authors found that their action was largely confined to the point of inoculation. These strains would produce a local keratoconjunctivitis if injected into the eye or a dermatitis when given subcutaneously and recovery was the rule without invasion of the central nervous system. Recovery is followed by an immunity to the virulent strains of herpes virus. They find that long glycerolation will frequently reduce the virus so that it is impossible to secure effective extracranial inoculation. The detection of herpes virus in the buccal secretions of healthy persons by rabbit experiment is unsuccessful and in the case of sufferers from labial herpes it is extremely difficult. The detection of the virus in cerebrospinal fluid is also attended with great difficulty, while the escape of the herpes virus through the urine is for the first time demonstrated by finding it in the urine in several rabbits. Another point brought out in the authors' paper is that, in spite of the known fact that one attack of virus infection affords almost complete immunity, it has not been definitely proven that the blood serum can neutralize the virus *in vitro*. Neutralizing substances occur in the blood of animals recovered from infection with the herpes and allied virus, yet are usually absent from human serum. "The conspicuous absence of the substance from the convalescent serum of cases of epidemic encephalitis argues against that disease being etiologically connected with one of the allied viruses." The series of papers close with a comparison of the clinical manifestations of the disease as it appears in man and rabbit.

The Sugar Content of the Cerebrospinal Fluid and its Relation to the Blood Sugar.—GOODWIN and SHELLEY (*Arch. Int. Med.*, 1925, 35, 242) found the cerebrospinal sugar content to be least fluctuant before breakfast, just as with the blood sugar. The cerebrospinal sugar exhibits much the same variations throughout the day (and in many diseases) as does blood sugar, although the peak rises following meals are not seen. The sugar in cerebrospinal fluid usually falls between 45 and 65 per cent of that in the blood regardless of the time of the determination. In diabetes, for instance, both fluids show roughly similar percentage sugar increases. It is obvious that sugar determinations on the cerebrospinal fluid alone at any time would be of little value. Encephalitis cases usually show a higher sugar content of the cerebrospinal fluid in relation to the blood sugar content, while in early cerebrospinal syphilis the opposite is found. Low actual and relative figures are also obtained in meningitis, whether tuberculous, staphylococic or meningococic in origin.

All-day-blood-sugar Curves in Non-diabetic Individuals and in Diabetic Patients with and without Insulin.—LEON JONAS, T. GRIER MILLER and IDA TELLER (*Arch. Int. Med.*, 1925, 35, 289) present a very valuable study of the all-day-blood-sugar variations, showing maximum rises shortly after the morning and evening meals much more frequently than after the noon day one. This occurs in most diabetic patients with much greater regularity than in normal individuals. Curiously enough, the morning rise is usually greater than the evening one, and reaches its peak about one hour after breakfast. For mild cases of diabetes on a maintenance diet divided evenly between the three meals, a single dose of insulin administered a half hour before breakfast sufficiently controls the blood sugar for the whole day. More severe cases require an additional dose, somewhat smaller, a half hour before the evening meal. If the morning fasting level of blood sugar is too high with the two doses, a third one is most effective given about midnight. This work brings out very nicely the value of proper timing of the insulin injections to yield a maximum control of the sugar metabolism.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

The Nomenclature Used by the Registry of Bone Sarcoma.—CODMAN (*Am. Jour. Roentgenol.*, 1925, 12, 105) states that for all intents and purposes, the person who presents himself with a bone tumor, which

is not inflammatory or metastatic, may be told that he has one of five tumors: Periosteal fibrosarcoma, prognosis fair with complete excision; benign osteogenic tumor, prognosis excellent with radical excision; osteogenic sarcoma, prognosis bad no matter what its treatment, although a few recoveries following amputation are on record; benign giant-cell tumor, prognosis good under almost any treatment, except bad surgery; Ewing's tumor, prognosis good for immediate reduction under roentgen radiation, but eventually bad; myeloma, certainly and slowly bad but probably retarded by radiation. All these types have their definite roentgen-ray criteria, and all these types have pretty definite microscopic and clinical characteristics. Cases of osteogenic sarcoma die pretty quickly whether they are fibro, chondro, osteo, round- or spindle-cell, and Ewing's tumor is no worse for being called multiple, diffuse, central, alveolar, perithelial or invasive.

The Cholesterol Content of the Blood in Relation to Genitourinary Sepsis.—MACADAM and SHISKIN (*Brit. Jour. Surg.*, 1925, 12, 435) say that in only about 50 per cent of the patients with a low cholesterol value, who subsequently died of pyelonephritis, did clinical opinion of the general condition of the patient contraindicate operation. In many instances, therefore, no certain information as to the resistance of the patient to postoperative spread of sepsis is afforded by considering the patient's clinical condition alone. The authors suggest that a low "blood cholesterol" in a case of acute or chronic retention due to prostatic enlargement is significant of a low capacity for antibody formation and points to the case being a bad operative risk as regards prostatectomy. Genitourinary sepsis with the risk of ascending infection is of more serious prognostic import than nitrogen retention from defective renal function. A high blood urea alone is not necessarily serious to ultimate prognosis—on the other hand, the combination of a high blood urea and a low cholesterol content is of very serious prognosis and points to an undoubtedly bad surgical issue.

The Surgical Treatment of Cleft Palate—DOWD (*Ann. Surg.*, 1925, 81, 573) believes that these children should have their defects repaired by the time speech is established. The operation on the lip should be done at the earliest practicable time. In many instances correction of the alveolar process and of the nasal deformity may be begun at the same time as the lip operation. The hard palate should ordinarily be repaired a few months after the primary operation on the lip and alveolar process. Metal plates and iodoform gauze packing are helpful in securing a good result. Usually the operation on soft palate should not be done until the hard palate has suitably united. The soft palate should be protected from traumatism and no tissues should be removed, excepting the small margin of the cleft. This repair should be accomplished at a single operation. It is the most delicate structure with which we have to deal. It should be conserved to the fullest possible degree. Speech instruction should be begun early and carried out persistently and carefully under skilful directions.

An Operation for Unreduced Posterior Dislocation of the Elbow.—SPEED (*South. Med. Jour.*, 1925, 18, 193) says that the operation is suit-

able in all uncomplicated posterior dislocations of the elbow, which have remained out a sufficient length of time to prevent closed reduction without undue trauma to the joint. After the second or third week closed reductions are generally not satisfactory. In the doubtful cases much less damage will be done and a much better functional result obtained by an open reduction. In cases complicated by extensive fractures and bony ankylosis an arthroplasty of the elbow offers the only hope of a movable joint. The author has employed the operation in a number of cases with most gratifying results. The amount of function depends upon the length of time the dislocation has existed and whether the case is an adult or child. Four of the cases were in children, three of whom had been injured between eight and twelve weeks. All of these obtained practically normal motion and a perfect functional result. One that had been dislocated eight months had about 60 per cent normal motion after six months. However, sufficient function had been reestablished to induce normal growth and development. One adult of ten weeks' duration, with the elbow in full extension and no motion in any direction, regained a complete range of supination and pronation and about 40 per cent flexion. A second adult with a dislocation of only six weeks' duration was making excellent progress at discharge. The technic and post-operative care are given in full in the article.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Factors Involved in the Acidity of Stools of Infants.—BROWN and TISDALL (*New York State Med. Jour.*, 1925, 25, 152) studied 1300 specimens for the determination of the pH of infants' stools. The pH of stools from normal, newborn breast-fed infants was found to be singularly constant, varying from 4.7 to 5.1. The acidity of stools from artificially fed infants was found to vary from pH 4.6 to somewhat more alkaline than pH 8.3. An acidity as great as pH 4.6 was encountered in artificially fed infants only in severe diarrheal conditions. Infants fed on butter soup generally had stools with an acidity of about pH 6.0. Infants fed on protein milk, cows' milk dilutions with added carbohydrate generally had stools more alkaline than pH 7.0 whole soured milk, with added carbohydrates up to a total content of 20 per cent, generally produced strongly alkaline stools. No difference was consistently observed in the acidity of the stool, whether the added carbohydrate was in the form of corn syrup, dextrimaltose or cane sugar. In this investigation the effect produced by other sugars was

not determined. The degree of acidity of the stools was generally increased in the presence of parenteral infection. The factors which influence follow. The acidity apparently depends on the ration in the intestinal zone of fermentation, of the carbohydrate on one hand to the protein and the base on the other. The amount of carbohydrate in the zone of fermentation, apparently is influenced by the extent of the zone of fermentation, by the type of carbohydrate, and by the state of health of the intestinal cells.

Effect of Pertussis on the Heart.—LEDBETTER and WHITE (*Jour. Am. Med. Assn.*, 1925, 84, 1022) remind us that heart disease, as evidenced in particular by valvular deformity, is occasionally found in young people without a history of rheumatic fever, chorea, repeated tonsillitis, scarlet fever or diphtheria, and in whom physical examination fails to show evidence of congenital defects of the heart or blood-vessels. Usually these patients show disease of the mitral or of the aortic valves or both, similar to that found after rheumatic fever or chorea. Even in the absence of a past history of such infections, it is often the custom to diagnose these cases etiologically as rheumatic in type. Sometimes it is possible by close questioning to discover that there was a probable rheumatic infection in childhood, often so mild that it may have been overlooked and diagnosed as growing pains. A mild chorea may have been called nervousness. Badly infected tonsils may be discovered. Even with diligent search there are some unexplained cases. A review of the literature and the expression from a number of pediatricists do not yield proof of endocardial or myocardial damage during or after pertussis. Circulatory failure does not seem to occur during pertussis, though the paroxysms of whooping cough undoubtedly do produce a temporary mechanical strain particularly on the right side of the heart. No evidence of damage to the heart in any case as a result of whooping cough could be found in a study of a series of 232 cases seen in the out-patient department of the Massachusetts General Hospital, and the Children's Hospital, Boston. However, one child had chronic endocarditis and had congenital heart disease before the infection. They were unable to find any evidence that whooping cough has a damaging effect on the heart.

The Ultraviolet Rays of the Sun.—HESS (*Jour. Am. Med. Assn.*, 1925, 84, 1033) feels that rickets affords an excellent criterion for the investigation of the biologic activity of the rays of the sun, for it is known within narrow limits the band of ultraviolet radiations that is effective in preventing or curing this disorder. A comparison of the yearly amount of actual sunshine in cities in the temperate zone demonstrates that there is no close parallelism between the incidence of rickets and annual sunshine. It shows that the occurrence of rickets does not depend on an equable distribution of sunshine throughout the year. In the Panama Canal Zone, where rickets is practically unknown, not only is the yearly sunshine less than in New York but it is even less evenly distributed. There are fewer hours of sunshine during the rainy season in Panama than during the corresponding winter period in New

York. The determining factor is the quality, not the quantity of the sun's rays. The amount and intensity of the short ultraviolet radiations alone are of value in preventing rickets. The results of heliotherapy during the winter months have been disappointing, owing to the fact that the antirachitic region of the solar spectrum is very limited at this season, and that the infants cannot be exposed directly to the rays of the sun on account of the severity of the climate. It would seem that the amount of the effective solar radiations is so small in winter that even if we substitute quartz panes for ordinary window glass, it will be insufficient to afford protection and eradicate rickets. The most promising therapeutic measures are ultraviolet light from artificial sources or the use of cod liver oil, or potent extracts of this oil.

Irradiated Foods and Irradiated Organic Compounds.—STEENBOCK and DANIELS (*Jour. Am. Med. Assn.*, 1925, 84, 1093) state that light can impart antirachitic properties to certain compounds, which furnishes the explanation why light acting directly on the body and cod liver oil taken by mouth can have the same action in preventing rickets. When light acts directly on the body, it acts in part by virtue of the fact that it activates antirachitically certain substances already present. Superficially considered, it thus becomes immaterial whether active compounds are ingested or whether they are activated after they are absorbed. The end result is similar. It may stimulate the question why antirachitic activity is not more generally distributed in foods ingested by man and animal, because plant materials can be produced only in the light by photosynthetic activity. This is probably no more peculiar than that rickets should occur at all, because just as foods are activated by exposure to light, it yields directly to light treatment. The explanation to this is to be found in the fact that solar radiation as it reaches the earth does not carry much of the ultraviolet rays, and it is only light found in this region of the spectrum that is active in this manner. This light has very little penetrating ability, so that plants unprovided as they are with any system for the translocation of lipoids cannot be affected to a high degree. Another question that arises but which is answered with more difficulty is what is going to be the future of irradiated foods and highly purified organic compounds? The answer to this may be anticipated on the basis of what is now known in regard to the effect of light of the proper wave length on various diseases. Of the possibility of their use in rickets, there remains no question, and it is not to be forgotten that rickets is only one form of disturbed calcium relation. By exposing such foods as wheat, rolled oats, corn, hominy, cream of wheat, shredded wheat biscuits, corn flakes, patent wheat flour, cornstarch, meat, milk and egg yolk to ultraviolet light, they can be endowed with antirachitic properties. That such a wide variety of foods can be thus affected appears to be due to the fact that practically all naturally occurring foods contain lipoidal constituents of the nature of sterols which can carry this activation. Cholesterol as obtained from the brain is entirely inactive, but after exposure to ultraviolet light becomes antirachitic. As fats are good solvents for these lipoids, practically all fresh fats such as butter fat, olive oil, lard, corn oil, coconut oil and cottonseed oil, can be activated, often to a degree to

make them compare favorably to cod liver oil. As antirachitic action consists in the induction of calcium assimilation and its conservation for the animal, this is a matter that concerns not only the young but also the adult. It is suggested that these findings may have their significance not only in nutrition, but also in the therapy of those diseases known to respond to irradiation with ultraviolet light.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY AT THE SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA,

AND

LOREN W. SHAFFER, M.D.,

ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE,
UNIVERSITY OF PENNSYLVANIA.

Mycotic Paronychia and Dermatitis.—KINGERY and THIENES (*Arch. Dermat. and Syph.*, 1925, 2, 186) report a new dermatomycosis occurring as an occupational dermatitis known locally as "fruit poisoning," occurring in certain canneries of the Northwest, particularly during the pear canning season. There is a rather marked paronychia characterized by inflammatory reaction, pain, and the actual loss of one or more nails. In addition maceration, vesiculation, and fissuring between and on the interdigital aspects of the fingers are frequently found and occasional patches of erythematovesicular dermatitis of the hands and forearms. Cultures from several patients have uniformly revealed pure cultures of a yeast like organism. Animal and human inoculations result in a clinical picture practically identical with known mycelial infections of the skin and exactly corresponding to the symptoms of patients suffering from the disease. This "fruit poisoning" may then be properly classified with the now known dermatomycoses.

Mouth Lesions of Erythematous Lupus.—CLARK W. FINNERUD (*Arch. f. Dermat. und Syph.*, 1925, 148, 318) quotes Trautmann as stating that mouth lesions occur in association with erythematous lupus, involving the buccal mucosa in 43 per cent of the cases; the gums, in 32 per cent, and the tongue, in 9 per cent. Finnerud describes a case in which the entire mucous membrane of the mouth was involved with periodic exacerbation, coincident with the use of a preparation known as Krysolgan. The mucosal lesions are raised red or bluish-white patches, often punctiform and linear in outline. The differential diagnosis includes corrosion of the mucous membranes by chemicals, stomatitis, leukoplakia, and the mouth lesions of lichen planus. The process in erythematous lupus shows no necroses, such as occur in

corrosive processes, and the mucous membrane is not diffusely swollen. Stomatitis likewise shows marked swelling and purulent discharge about the niches in the gums, which does not occur in erythematous lupus. The process is differentiated from leukoplakia by the presence of telangiectasis in erythematous lupus with inflammatory changes, which are absent in leukoplakia. The most pronounced leukoplakia is rarely diffuse and the gums are likely to remain free. Central atrophy of the mucosal patches in erythematous lupus may occur, which also distinguishes it from leukoplakia. Epithelial thickening of lichen planus is more sharply defined. There are occasional annular figures and very little inflammatory change. In lichen ruber pemphigoides small erosions may be found. Lichen planus of the mucous membranes presents no subjective symptoms, while burning pain, and dryness of the mouth are the rule with erythematous lupus.

Amyloidosis of the Skin.—H. KÖNIGSTEIN (*Arch. f. Dermat. und Syph.*, 1925, 148, 330) describes miliary papular amyloidosis of the skin in association with general amyloidosis. The clinical picture consists of small papules and nodules in the skin, most conspicuous about the eyelids, on the forehead, along the vermilion border of the lips, on the palms of the hands, and the dorsums of the feet. The papular and nodular infiltrations about the genitalia are strikingly shown in mouldages. Practically no portion of the skin is completely exempt except the dorsal surfaces of the hands and the plantar surfaces of the feet. The patient was a man, sixty years of age, who, following erysipelas of the face, had had pain in the shoulders and extremities for two years, coincidentally with an abundant crop of the hard nodules already described. There were no cutaneous subjective symptoms associated. Somewhat later, erosions on the mucous membranes appeared with intestinal disturbances and cachexia. Atrophy of isolated muscle groups developed. The intestinal picture was associated with symptoms of peritonitis and ileus. In addition to the general miliary papular lesions, larger tumors were found in the fascia and musculature. A diagnosis of amyloid was made histologically, and the postmortem demonstrated the universality of the involvement. A second case is described, and the literature of the condition reviewed. Localized amyloidosis of the skin has been described by Herxheimer, Gutmann, and others. The clinical resemblance to lichen planus is mentioned.

Investigations into the Isolation and Chemical Composition of Trichophytin, the Active Antigenic Principle of Pathogenic Molds.—BR. BLOCH, A. LABOUCHÈRE and FR. SCHAAF (*Arch. f. Dermat. und Syph.*, 1925, 148, 413). Trichophytin is the substance which can be isolated from pathogenic molds and which gives rise to cutaneous sensitization reactions and, in all probability, to the general allergic or sensitization manifestations produced by these fungi in the patient. Bloch and his collaborators have done an extremely interesting and important work in attempting to isolate the pure substance. While their effort has not been wholly successful as yet, they feel that they can now define trichophytin as a nonprotein substance, which can be dialyzed through a parchment membrane and appears to be in close combination with a water soluble, nitrogen containing polysaccharid.

Its total nitrogen content is approximately 6.75 per cent, amino-nitrogen, 1.3 per cent. The authors are not yet prepared to state that the polysaccharid is the active principle itself but provide in their discussions for the possibility that the nitrogen containing element may be physically bound or absorbed by the polysaccharid. The substance is extremely stable and physiologically active.

Painful Nodular Growth of the Ear.—O. H. FOERSTER (*Arch. Dermat. and Syph.*, 1925, 2, 149) reports 12 cases of this condition, the lesion consisting of a small nodular painful growth on the rim of the ear, usually on the upper pole in the region of the crown angle. The growths are single, ovoid or circular, well defined and firm nodules, varying from 3 to 10 mm. in their longest diameter. They are imbedded in the skin or elevated several millimeters above the surface and usually firmly attached to the cartilage. They often show a central depression and a surrounding zone of hyperemia. Pain is a characteristic feature. It may be quite acute, preventing the patient from resting the head on the affected side or awakening him from sleep. Histologically the lesion presents an inflammatory reaction of unusual diffuseness and depth, intense edema, and degeneration of both collagen and elastic tissue. The etiology is unknown. Excision of the nodule inclusive of the cartilage is the treatment of choice. Roentgen ray and radium usually give relief, but recurrence is frequent.

Experimental Studies on Eczema.—KLAUDER and BROWN (*Arch. Dermat. and Syph.*, 1925, 2, 283). The purpose of this study was to repeat the experimentation of Luithlen concerning the influence of diet and metabolism of bases with particular reference to the calcium balance in relation to skin sensitivity. Their experiments on rabbits and cats to standardized external irritation showed that the cutaneous irritability was altered by diet, injections of drugs and colloidal substances, by narcosis and experimentally produced nephritis and hepatitis. Such altered cutaneous sensibility could not definitely be correlated with blood chemistry studies and especially the calcium content of the blood. However, they obtained some evidence that metabolism of basic substances, particularly calcium, plays a role in determining altered sensibility of the skin. Rabbits under the influence of a diet rich in albumin will react very much more definitely to irritation than those on green fodder diet, and the animals to which salts of calcium are given acquire a decreased sensibility to irritation of the skin. Their observations would tend to show, however, that other factors are concerned in addition to the metabolism of bases.

On the Treatment of Syphilis of the Aorta.—H. SCHOTTMÜLLER (*Am. Jour. Syph.*, 1925, 9, 1) is an advocate of intensive treatment of all types of aortitis with arsphenamine and mercury. He makes the radical statement that intensive treatment is always indicated, never harmful. He classifies aortitis as aortitis coronaria, aortitis supracoronaria and aortitis valvularis. Aortitis coronaria is often amenable to treatment. Aortitis supracoronaria affords the most favorable prognosis. Syphilitic insufficiency of the aorta in its early stages is a curable condition so long as cardiac hypertrophy remains the only

physical sign. Aortitis valvularis constitutes the most dangerous form of this affection. A cure from the anatomic point of view can only be expected in the early stages of the disease. He opposes symptomatic treatment and a preparatory period on mercury as a waste of valuable time by withholding arsphenamine treatment. Treatment consists of weekly injections of neoarsphenamine 0.45 to 0.6 gm. for a total of at least 5 gm. followed by a rest interval of two months on potassium iodide. Mercury is given simultaneously either by weekly intramuscular injections of calomel or mercury salicylate or a soluble mercurial intravenously. The patients are then kept continuously under the influence of arsenicals for two to three years, being given an intravenous injection of 0.45 to 0.6 neoarsphenamine every four weeks or repeating the above course twice yearly. This article presents many points of interesting contrast with current views.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Five Cases of Pregnancy with Abdominal Myomectomy.—GOULLIoud (*Gynéc. et Obst.*, 1924, 9, 268) reports five cases of myomectomy occurring during pregnancy. The first was in a woman, aged twenty-seven years—a large tumor from the posterior surface of the uterus at the fundus. This was removed before the patient's pregnancy, and the question arose whether from the size of the tumor pregnancy and successful parturition would be possible. The patient made a good recovery, and was told that she might marry. Some years later she had a normal pregnancy followed by spontaneous childbirth, and again suffered from hemorrhage with symptoms of a return of the growth. At this time she was treated by two tubes of radium, 120 mg., for twenty-four hours, followed by the cessation of the hemorrhage and the diminution in size of the tumor. The second patient had an abortion at four months, followed by a spontaneous labor, and at that time it was discovered that she had a fibroid tumor. The tumor was interstitial on the anterior wall and was removed, and the patient had some fever after the operation. Hematoma followed in the right lower quadrant, which simulated appendicitis. She recovered and afterward had an early abortion and then another pregnancy. She entered the hospital for confinement and was successfully delivered of a living child. On her recovery no evidence of fibroid tumor could be found. The third case had an abortion at six months and was found to have a uterine fibroid. Myomectomy was difficult, but was performed and the patient made a good recovery, complicated by a stitch abscess which persisted for some time. She afterward had a spontaneous labor and successful recovery, and six years after the operation

was in good health. In the following year she was found to have a fibroid the size of an orange and the uterus was extirpated. From this she made a good recovery, and on examination the uterus was found to contain many interstitial fibroids. The scar of the first operation was sound and complete healing had occurred. The next patient had an early abortion at two months followed by another at five. There was a uterine fibroid of considerable size and this was removed. Following this there was another abortion, and an effort was made to thoroughly examine the patient, but she passed from observation. A case is cited in which five pregnancies in succession were successful following the removal of a fibroid of considerable size. The removal of a fibroid on the anterior wall and the emptying of ovarian cysts occurred in a patient who had a three months' abortion later. Following this there were signs of return with hemorrhage, and the patient was treated by radium. He reports several cases where the removal of the fibroid was followed by successful pregnancy. One patient had decided not to marry because she had a fibroid tumor of considerable size. She became anemic, and operation was necessary which was successfully carried out and a large tumor removed. The patient, married and gave birth to a deformed child which did not long survive and this was followed later by a spontaneous birth of a healthy living infant. An interesting case is reported in which a patient had a fibroid tumor and also a cyst in which operation was done in early pregnancy, and the pregnancy was not suspected. It was not interrupted and the patient went on to full term, when she entered the hospital with a child in shoulder presentation. This was corrected by external manipulation, but hemorrhage followed and placenta previa was present. A still-born child was delivered by version, and the mother recovered from the labor. A patient, aged thirty-five years, had a myomectomy followed by pregnancy, prolonged labor, application of the forceps and death from septic infection. An extraordinary case is reported in which a patient had a fibroid tumor complicating pregnancy and an abortion. Myomectomy was performed and, on examination, it was thought that the tumor was malignant. The patient recovered and again became pregnant, with placenta previa. On examination it was found that a small fibroid had developed in the broad ligament, which rendered vaginal delivery impossible, and the patient was delivered by section and the uterus extirpated. The child survived the operation, and the mother had a ureteral fistula which required nephrectomy and the opening of an abscess in one of the broad ligaments. She finally, however, made a recovery. From a study of his cases the writer concludes that 25 per cent of women having fibroid tumors of the uterus and exposed to impregnation become pregnant, and that among married women the age of these patients is usually less than forty years. He believes that if women, aged about thirty years, having fibroid tumors of the uterus have these tumors removed successfully they are competent to pass through pregnancy and parturition successfully. The obstetrician may then propose myomectomy to women of a child-bearing age with a good prospect of success. If at operation he found myomectomy to be impossible he can advise hysterectomy or close the abdomen and treat the patient by radium or the

roentgen-ray. In labor following myomeetomy there is no special difficulty provided the uterine wound has soundly healed. It must be remembered that most myomeetomies are done upon primiparæ beyond the usual age of childbirth, and that in such patients labor is usually prolonged and difficult. One cannot rule out the possibility of small fibroids in the cervix, whose existence may not be detected until operation, and which render the development of pregnancy difficult and spontaneous labor impossible. Malignancy in a fibroid must also be taken into consideration. Patients who have had myomeetomies, but have afterward become pregnant, must be cautioned to go to the hospital for confinement, for complications may occur which require surgical help. In some cases fibroid tumors may develop in the uterus as late as ten years after myomeetomy. Radium or the roentgen-ray may then be successfully employed to check the growth of such tumors. The next is a curious case of double uterus with fibroma, pregnancy in one half, treated by hysterectomy. DAMBRIN and BERNARD BEIG (*Gynéc. et Obst.*, 1924, 9, 293) report the extraordinary case of a woman, aged twenty-seven years, whose history was unimportant and who had been married about a year when she sought medical advice. A hematoma in the vulva had developed which suppurated and required opening, and the patient complained of considerable pain. On examination the abdomen was enlarged and painful; there was a sensation of weight in the lower abdomen and a leucorrheal discharge. Menstruation had ceased about three months before; pain had increased; the abdomen had grown in size, and the patient suffered from constipation, nausea and vomiting. On inspection the abdomen contained a globular tumor in the median line, painful on pressure. There were two vaginal openings: The one on the right of normal size and the one on the left small and retracted. On the right side a cervix was found which was that of the pregnant uterus. The right side of the uterus was found enlarged, and the separation of the two vaginæ terminated at the uterine neck. There was a small cervix and tumor on the left side. The patient was in bad general condition, and a diagnosis was made of a small ovarian cyst complicating pregnancy. At operation a double uterus was found with a fibroid on one side and pregnancy on the other. The side containing the fibroid was removed and the side containing the pregnancy was not disturbed. The examination of the tumor removed showed an edematous fibromyoma. The patient recovered from the operation and later gave spontaneous birth after a somewhat prolonged labor to a healthy living child, weighing 2050 gm.; the child was normally developed. The partition between the two vaginæ was removed by the labor. The writer adds a detailed review of this case illustrated by drawings.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Fibroid Tumors of the Vulva.—Fibroid tumors of the vulva are uncommon, although they are the most frequently observed benign solid tumors of this region. In reporting an interesting case of this type, FULLERTON (*Surg., Gynec. and Obst.*, 1925, 40, 244) presents a nice discussion of the subject which we shall briefly abstract. The tumors occur almost invariably during the child-bearing period, although they do occur later and have been observed in infants. Virgins and parous women seem to be about equally affected. The tumors are usually single and are first seen as small, firm rounded and smooth or slightly lobulated, painless subcutaneous masses. The smaller ones, especially if deep, may easily be overlooked. Pedunculation is common, particularly in the larger tumors. Growth may be rapid, although it is more often slow. Interference with locomotion or discomfort from position send the woman to the surgeon. The skin over the tumor is wrinkled, often more or less pigmented, and freely movable. Because of the increased vascularity of the parts during menstruation and pregnancy, more rapid growth is often noticed at these times. Ulceration is rare, although such a complication occurs from interference with the blood supply or external irritation. Degeneration and malignant transformation are more common in these tumors in this location than in similar tumors located elsewhere in the body, probably because of their variable blood supply, pedunculation and position, which makes trauma more or less unavoidable. Edema, hyalin and cystic degeneration, calcification, ulceration, infection and sarcomatous transformation have all been observed in these tumors. They originate in the connective tissue and may start anywhere in the vulvar structures or in the extraperitoneal portion of the round ligament or internal genitalia, and as they increase in size they are forced into the line of least resistance down the inguinal canal or vagina and appear at the vulva.

Treatment of Pelvic Suppuration.—While we cannot endorse the method of treatment which WORRALL (*Surg., Gynec. and Obst.*, 1925 40, 174) employs in cases of pelvic suppuration, it has given him such satisfactory results in his service in the Sydney Hospital that we present it for those who may be interested. According to his method when there are indications of the presence of pus or any acute, pelvic condition, a preliminary vaginal celiotomy is made, usually posterior to the uterus, into Douglas' pouch, but when the physical signs point to the collection being anterior to the uterus, the bladder is dissected up and the entry made into the uterovesical pouch. The

pus is evacuated, the pus sacs are defined and punctured, and a large split rubber tube is inserted and stitched in the opening. The tube is split in order to lessen the danger of pressure necrosis of the inflamed, softened bowel. Iodoform gauze is sometimes used in addition, but never passed into the tube. In forty-eight hours after this operation the constitutional symptoms have usually undergone a great improvement, and at the end of a week, or perhaps a few days more, the patient having eliminated the toxins, feels well. She then undergoes the second stage of the operation. After removal of the gauze and the tube, the drainage tract and vagina are cleansed with 25 per cent hydrogen peroxide, and abdominal section is performed, the suppurating focus removed and a fresh drain placed through the vagina. Under this plan of treatment all acute pelvic conditions, except the first attack of a mild gonorrheal salpingitis, are operated upon without delay; if the patient is very ill, on the day of admission. "Waiting for the temperature to settle down and the pus to lose its infectivity" has not been practised. Should one fail to evacuate pus by the vaginal incision, abdominal section is performed at the same sitting, the offending focus removed and vaginal drainage established. The writer states that he always practises vaginal celiotomy preliminary to abdominal section, when there is reason to anticipate a considerable number of adhesions or unusual difficulties from past infection. Iodoform gauze is passed into the wound in the vaginal vault, and this is a landmark in carrying out the removal of the focus from above. When the writer presented this paper before the American College of Surgeons the American gynecologists who discussed it were unanimously opposed to the procedure.

Importance of Urethral Prolapse in Women.—On account of the frequency of confusion in diagnosis between urethral caruncle and urethral prolapse in women, and especially on account of the importance of the latter condition as a symptom of disease higher in the urinary tract, CHUTE (*Boston Med. and Surg. Jour.*, 1925, 192, 162) reminds us that the term urethral caruncle should be limited to the little raspberry-like growths that are seen at the meatus. They are true papillomas of the urethra and produce stinging on urination, occasionally a little urethral bleeding and sometimes even a little urethral discharge. They rarely produce marked symptoms of bladder irritation or any considerable amount of bleeding. He cites three cases which had previously been operated upon for "urethral earuncles" but later developed bladder tumors, and he is of the opinion that the so called earuncles were probably cases of prolapse of the urethra due to vesical straining. The point which he desires to emphasize is that we should be very cautious in accounting for marked urinary symptoms in women as due to the presence of a relatively minor urinary lesion at the meatus. Cases of this sort should be subjected to careful cystoscopy examination before any operation is performed. In cases where the basic trouble is a self-limited inflammatory lesion of the bladder the patient will often improve so much during the convalescence following the operation for the removal of the urethral lesion as to make it seem probable that the relief depended upon the operation, but in cases where the bladder lesion is a serious one, such as a tumor, valuable time will be lost.

RADIOLOGY

UNDER THE CHARGE OF

RUSSELL D. CARMAN, M.D.,

HEAD OF THE SECTION OF ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

A Summary of the Effects of Repeated Roentgen-ray Exposures upon the Human Skin, Antecedent to the Formation of Carcinoma.—S. B. WOLBACH (*Am. Jour. Roentgenol. and Rad. Ther.*, 1925, 13, 139) describes the earliest histological changes found in the skin of guinea pigs and rats as early as forty-eight to seventy-two hours after experimental exposure to roentgen rays, and a striking swelling of the collagen fibrils of the corium, subcutaneous tissue, and the walls of bloodvessels. The epidermis shows no change until the swelling of the collagen fibrils has occurred. The lesions of the epidermis appear to be secondary to the obliteration of the lymphatics and capillaries, caused by the swollen collagen. The maximum effect of radiation is upon the superficial layers of the corium. The initial change appears to be a focus of localized edema immediately below the epidermis separating the epidermis from the viable corium and later a necrosis. The gap is covered by regeneration of the epidermis which becomes altered and migrates downward because of incomplete nutrition. This effect is noted by a thickening and keratinization of the epidermis. This proliferative activity of the epidermis greatly in excess of normal proliferation may be an outstanding fact in the origin of epidermoid carcinoma in chronic roentgen-ray dermatitis. The acquisition of malignant properties is not of sudden onset but acquired in the course of years.

The Normal Movements of the Stomach.—In reviewing the literature, McCRAE, McSWINEY, MORISON and STOPFORD (*Brit. Jour. Rad.*, 1925, 30, 48) found a great diversity of opinion in regard to the normal movements of the stomach. There are two main schools: the first believes that the typical gastric movement consists of two distinct phases: (a) Peristaltic wave which involves the body of the stomach and preantral region; (b) a contraction of the musculature of the pyloric antrum as a whole. The second school believes that the peristaltic wave sweeps from its origin on the body of the stomach to the pylorus and does not partition the stomach. Cole attempts to correlate the two schools and classifies the different types of peristalsis under the headings of: (a) One cycle; (b) one-and-a-half cycle; (c) two-cycle; (d) three- and four-cycle; (e) choreic type. The authors examined rabbits, cats and dogs by direct observation under anesthesia and by roentgen-ray examination. The human was studied only by roentgen-ray examination. This work confirms the existence of two distinct types of movement which correspond closely to that described by the two schools. They have in addition observed in a few cases a third variety in which the shallow waves pass on over the formed antrum and is regarded as occupying an intermediate position between the other two types. The

results obtained by direct examination have in great part been substantiated by roentgen-ray findings. The authors believe it probable that the type of movement present is to some extent governed by: (1) The consistency and type of food; (2) the degree of tension of the wall of the organ; (3) the muscular formation of the stomach wall. Their conclusions are as follows: (1) The form of movement known as the two-phase type is that most frequently found in the stomach of man, the dog, and the rabbit; (2) the form of movement known as the one-phase type, or some modification of this, is normally found in the stomach of the cat; (3) either form of movement may on occasion be observed in the stomach of man, the cat, and the rabbit; (4) the movements of the corpus ventriculi and of the pars pylorica may occur with differing rhythms.

Light Treatment in Medicine.—AXEL REYN (*Radiology*, 1925, 4, 288). In addition to the visible rays in white sunlight there are some invisible ones, the ultraviolet and the infra-red; the ultraviolet have a chemical effect and certain biologic effects on the living organism. In accordance with Finsen's ideas, light is concentrated through lenses for local treatment, and nonconcentrated for exposing the whole body to light baths. For local treatment Finsen used the carbon arc light exclusively for it contains far more ultraviolet rays than sunlight, the ultraviolet rays of which are absorbed by the atmosphere. The installation used for local treatment consists of a 50-ampere carbon arc lamp; hanging around this are four convergent lenses for concentrating the light. The lenses are made of rock crystal, which, unlike ordinary glass, does not absorb ultraviolet rays. For absorption of the heat rays, a layer of water is placed between some of the lenses. In order to prevent absorption of the chemical rays by blood the skin must be made bloodless. This is done by compressing apparatus, by means of which blood is pressed away from the spot to be irradiated. Marked success has been obtained in the treatment of lupus vulgaris, 60 to 70 per cent of permanent cures resulting. Acne vulgaris et roseacea, alopecia areata, roentgen ulcer, xanthelasma and trachoma have also been treated in this manner with varying grades of success. For light baths artificial light must replace sun light in Northern countries, and for this purpose carbon arc lamps are used, with direct current. Hasselback pointed out that skin erythema brought about a fall of blood pressure in the bloodvessels in the periphery and caused deeper inspiration. Therefore, he believed in the light bath treatment of heart disease. Its greatest value is, however, in the various forms of tuberculosis. Often lupus vulgaris has to be treated with light baths in addition to local treatment. Out of 114 cases, 96 were cured by the author by the combination of local treatment and light baths. The results obtained in the treatment of cases of surgical tuberculosis by carbon-arc-light baths "are most astonishing." In tuberculosis of the elbow, for example, 93 per cent cures were obtained. In tuberculous glands, 95 per cent of 500 cases have been cured. Great benefit was also obtained in rhinolaryngologic tuberculosis. The effect of light on tuberculosis cannot be definitely explained. There have been many explanations but the author classes them as merely hypotheses. Nontuberculous diseases are also treated by light baths, among them being hypertension, neurasthenia, simple anemia and rickets.

Radiographic Diagnosis of Periapical Dental Infection.—Cultures were made of the periapical tissues of 1307 vital and pulpless teeth, and the findings compared with the radiographs by RUSSELL L. HADEN (*Radiology*, 1925, 4, 337). Of 392 vital teeth 9 per cent showed from 1 to 10 colonies in a deep agar tube, 5 per cent 10 or more colonies and only 1 per cent over 100 colonies. Ten per cent of 490 pulpless teeth negative in the radiograph, showed from one to 10 colonies, 44 per cent had 10 or more and 24 per cent had over 100 colonies. Of 425 pulpless teeth with positive radiograph, 10 per cent showed from 1 to 10 colonies, 60 per cent 10 or more and 44 per cent had over 100 colonies. The incidence of infection is almost as high in the radiographic negative group as in the radiographic positive one. There is a very sharp limitation to the translation of radiographic evidence of infection into terms of bacteria. The absence of radiographic evidence of infection at the apex of a pulpless tooth never excludes the presence of active infection. In many cases the radiographic negative tooth is a far greater source of systemic infection than the radiographic positive tooth, since in the former there may be little resistance to infection.

The Treatment of Tuberculosis of the Female Genitalia with Light and Rays.—HENRY SCHMITZ (*Radiology*, 1925, 4, 283) states that genito-urinary tuberculosis of the female is a local manifestation of a generalized tuberculosis, usually secondary to primary disease in the respiratory or digestive tract. Treatment therefore must be directed toward the disease and not merely toward a local manifestation. The methods of treatment are medical and surgical, each with a curability of 33 per cent, and actinic. The last method consists in the daily application of a light bath of an hour's duration from an Edison carbon light diffused by a reflector. The anterior and posterior body surfaces are each exposed for one-half hour. This is followed by the application of the ultraviolet ray obtained from an air-cooled quartz light, according to Rollier's method. The head is always covered. The body is divided into five parts. A table is given showing the time duration and fields, the time being increased until exposure of fifteen minutes are given daily over anterior and posterior surfaces. A pronounced tanning is produced. Treatment is given every other day, and twice a week for an entire year when local healing has been obtained. If necessary, Roentgen-ray therapy is added to the ultraviolet-ray treatment. If after the second roentgen-ray treatment the general and local condition is not markedly improved, the case is considered refractory to actinic therapy. This does not interfere with surgical procedures that might be indicated. General treatment also must not be neglected. Two case reports are given.

Pneumonokoniosis in the Ruhr.—Twelve cases of pneumonokoniosis with roentgenograms are reported by A. BOHME (*Fortschr. a. d. Geb. d. Roent.*, 1925, 33, 39). Three were in coal miners and 9 in stone masons. As depicted in the roentgenogram the extent and localization of the process varied among the different cases. In 3 the lateral portions of the lungs were chiefly affected; several had marked involvement of the apices. In most cases the lowermost portions of the lungs were spared. Tuberculosis was a complicating factor in 3 cases.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO; TORONTO, CANADA,

AND

W. L. HOLMAN, M.D.,

ASSISTANT PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA.

Experimental High Intestinal Obstruction in the Monkey.—In previous papers HADEN and ORR (*Jour. Exper. Med.*, 1925, 41, 107) have reported the essential changes, as they have found them in the blood and urine of man and dog in intestinal obstruction as a primary fall in blood chlorides, usually a rise in alkali reserve, and finally a rise in non-protein nitrogen. The chemical and clinical evidences of toxemia do not appear until the chlorides are well depleted. This paper deals with experimental high intestinal obstruction, aseptically performed, in 5 monkeys. The obstruction was obtained by section and inversion of the cut ends, and an autopsy was always performed to rule out peritonitis. Observations on the blood were made twenty-four hours before operation and at twenty-four-hourly intervals thereafter until death. For purposes of comparison they present the blood chemistry findings in 13 normal monkeys. These findings vary very little from the average normal in man. No vomiting was observed in the experimental animals, though there was a marked fall in blood chlorides in 2 of the monkeys and a less marked but definite fall in the chlorides of the other three. This emphasizes the fact that vomiting alone does not account for the fall in blood chlorides characteristic of intestinal obstruction. All animals showed a marked rise in non-protein nitrogen and coincident with the fall in blood chlorides there was a rise in CO₂ combining power. The uric acid and creatinine showed no typical changes. In a further study of the chlorides, *The Distribution of the Chlorides in the Blood of the Dog after Experimental Intestinal Obstruction* (*Jour. Exper. Med.*, 1925, 41, 113), the same authors determined the chlorides simultaneously in whole blood in plasma and in the cells, using the van Slyke method. Four animals were used and they all showed the characteristic fall in blood chlorides, this decrease being shown more characteristically in whole blood than in cells or plasma. (The idea of using whole blood in chloride determinations by an ashing procedure is a comparatively recent one of van Slyke's.) It is shown that the fall in chlorides is born almost equally by the cells and the plasma, and that the estimation on whole blood is more desirable than on plasma. It is also demonstrated that the disappeared chlorides do not exist in the blood in some undetermined form and that they must be sought for elsewhere. The findings were compared with those obtained by the iodometric titration on protein-free filtrate and were found to check very closely. Following this, HADEN and ORR (*Jour. Exper. Med.*, 1925, 41, 119) reported further on the same subject in *The Sodium Content of the Blood of the Dog after Experimental Intestinal Obstruction*. They wished to determine

if possible whether the sodium freed from combination with the chloride is recombined in the form of carbonate, is lost from the blood, remains free or is combined in some other manner. Ten animals were used, and the methods followed were the same as those previously reported (*vide supra*). All animals showed the characteristic rise of non-protein nitrogen, and the CO_2 combining was always increased. Relatively little change in the sodium content was found however. It tended to rise rather than fall. The findings do not support the theory that the increased destruction of body tissues is due to accelerated autolysis following the withdrawal of sodium from body protein. The experiment shows that the loss of acid radicles is not accompanied by a loss of basic, and the manner in which the excess of basic is combined was not determined. No light was thrown on the mechanism of the increased protein destruction characteristic of intestinal obstruction.

Encephalitozoön Cuniculi as a Kidney Parasite in the Rabbit.—The importance of the study of the Encephalitozoön cuniculi (so called "Cameron body") is emphasized by SMITH and FLORENCE (*Jour. Exper. Med.*, 1925, 41, 25). In reviewing the literature they find that the parasite has been described by Wright and Craighead in the central nervous system, kidneys and urine of rabbits suffering from motor paralysis; by Levaditi, Nicolau and Schwen in the central nervous systems of rabbits used by them in a comparative study of the virus of encephalitis obtained from four different sources, and later in the kidneys of 3 rabbits inoculated with virus from a spontaneous case; by Doer and Zdansky in the brains of 8 out of 224 rabbits. Kling and later Oliver also reported it in rabbits' brains, and recently Goodpasture has described it in the brains and kidneys of rabbits suffering from spontaneous encephalitis. (Reviewed by Da Fano in *Medical Science*, 1923, 10, 355.) The authors describe the parasite in 45 out of 163 rabbits autopsied. The disease appears to be endemic with an increase in the number of cases in the early summer. It was found in young rabbits only. No characteristic symptoms were presented. When recovered from the kidneys the parasites appear as pale or more highly refractive bodies of rod-like outline 2.5 to 3 mm. long and 1.5 to 2 mm. broad, somewhat Gram-positive and non-acid fast. They occur in dense groups within epithelial cells or singly in the debris in affected tubules. The parasite has the appearance of two coccoid end forms with a slender connection between roughly the form of a figure eight. Variations in the morphology are described. The collecting tubules near the tip of the papilla seem to be the most consistently invaded. The authors offer evidence for and against the status of the organisms as a bacterium or a protozoön, with the balance in favor of the protozoön, and they go on to offer a tentative life cycle. The parasite has been developed in the mouse and the dog. The pathology of the condition insofar as it is at present known seems to be a mechanical blocking of the normal flow of urine from the convoluted tubules and the descending limbs of Henle's loops, leading to dilatation and ultimate cellular reactions. Lymphoid-cell infiltration was noted in the kidney cortex. Lymphocytic filtration was found in various portions of the brain, but localization in the brain

could not be correlated with the cellular reaction. The kidneys are looked upon as the normal habitat of the parasite, while the brain is outside the normal cycle. The authors indicate many attractive ways in which the problem may be further studied.

The Serological Classification of the Tubercle Bacilli by Agglutination and Absorption of Agglutinins.—A series of experiments on the agglutination reaction and the absorption of agglutinins was conducted by G. S. WILSON, University of Manchester (*Jour. Path. and Bacteriol.*, 1925, 28, 69) to ascertain whether serological differences could be substantiated between the human and the bovine types of tubercle bacilli, whether the human bacilli could be subdivided into serological classes and whether these tests differentiate human and bovine types from other acid-fast bacteria. The investigations were carried out with eighty-nine strains of avian, bovine, human, reptilian and saprophytic acid-fast bacilli, the strain being collected from a great variety of sources. The results of the agglutination tests showed that there was a considerable amount of cross agglutination in the case of every serum, although the avian type showed a fair degree of specificity. With the human and bovine types, however, the specificity was so slight as to be valueless. As it became clear that there was but little differentiation in the direct agglutination test, attention was given to the absorption of agglutinins. The series of experiments showed that the bovine and human strains are indistinguishable serologically. Furthermore, no evidence was found of a multiplicity of types among the human strains tested. The authors concluded, on the basis of the absorption test, that the human type is a homogeneous one and that the bovine and human strains possess a fundamental identity of structure. The investigation showed incidentally that certain well-known strains of tubercle bacilli are masquerading under a wrong denomination. Such a strain as the Koch-Nathian raw strain (the same as the H34 of the author's collection) has been shown to be not a human but an avian strain.

A Peculiar Staining Reaction in Red Blood Cells.—ECKSTEIN (*Virchow's Arch. f. path. Anat.*, 1924, 249, 118) found that by using the Alzheimer methylene-blue-eosin method of staining that the erythrocytes ordinarily stain red. He observed, however, in other instances, particularly in areas of hyperemia and hemorrhage that the staining reaction was variable, some of the cells being red, others blue. Various gradations between these colors were commonly seen. He has been able to show that the red blood cells when free of carbon dioxide stain red, but when an appreciable amount of carbon dioxide was present at the time of fixation the reaction is blue. This reaction gave satisfactory results, even when the hemoglobin was reduced or when other gases had been absorbed. This finding may explain the reason for the variable staining qualities exhibited by red blood cells in tissues which have been sectioned.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. MCCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Rocky Mountain Spotted Fever: Experimental Studies on Tick Virus.—SPENDER and PARKER (*Pub. Health Rep.*, 1924, 39, 3027-3040) review the considerations relative to the natural evolution of Rocky Mountain spotted fever as follows: (1) The disease is maintained in rodents and ticks; human cases are secondary and accidental. (2) The disease exists in definite foci, and the virulence of the infection may vary decidedly even in adjacent areas. (3) A large number of rodent species are susceptible, but there is no evidence that the infection is highly fatal among them. (4) The complete life cycle of the tick includes four stages, and the infection may pass from stage to stage and from one generation to the next. (5) A disintegration of tissue (histolysis) takes place during the premolting period of larvæ and nymphs. (6) The tick ingests mammalian blood three times during the cycle—twice from small rodents (most of them susceptible to spotted fever) as larvæ and nymphs and once from large animals (all immune as far as known except that some adults feed on jack rabbit, snowshoe rabbits, and porcupines, of which animals at least the first two are susceptible to spotted fever) as adults. (7) The virus passes through the egg and larval stages of the tick in one summer, but in the unfed nymphs and adults it has been compelled to adapt itself to the hibernation (also estivation in the adult) which these stages undergo.

The results of the new work is summarized by the authors as follows:

- (1) In confirmation of earlier observations of previous workers, ticks of the species *D. andersoni* which have received the infection of Rocky Mountain spotted fever in the larval or nymphal stage retain it in the adult stage.
- (2) A twenty-four hour incubation at 37° C. of unfed hibernating nymphs and adults infected as larvæ and subsequent injection of emulsions of such ticks into guinea pigs give a higher percentage of positive infection than the injection of similar ticks not incubated.
- (3) Infection of Rocky Mountain spotted fever in adult ticks subjected to winter temperatures (32° F. or below) may be demonstrated by the production of immunity in guinea pigs following the injection of tick viscera immediately upon removal from cold temperatures, by a moderate but typical spotted fever following the injection of ticks after twenty-four hours incubation at 37° C., and by virulent spotted fever following tick feeding or the injection of ticks after feeding.
- (4) Control adult ticks free from all infection do not produce death or

illness in guinea pigs by feeding nor by injection of such ticks after feeding. (5) One infected adult tick may contain after feeding, from 3000 to 5000 M. L. D. for a guinea pig. (6) Emulsion of infected fed adult ticks treated with 0.5 per cent phenol will protect guinea pigs against 1 cc of blood virus. (7) Nothing in the behavior of blood or tissue virus is comparable to the changes observed in tick virus.

State-wide Milk Sanitation Program.—FRANK (*Pub. Health Rep.*, 1924, 39, 2765-2777) states that most municipalities fail to take the necessary steps to safeguard milk supplies unless guided by the State health organization. He considers milk as second only to water in the transmission of disease and lays emphasis on the need for its sanitary supervision. The steps taken in Alabama to reach the desired end were (1) To develop an effective type of milk legislation. (2) To encourage the cities of Alabama to enact it. (3) To insure its effective enforcement; and (4) to measure its results. Safe milk is defined as high-grade milk, pasteurized. The details of the means of providing a safe supply are given.

Diabetes Mellitus. A Contribution to its Epidemiology Based Chiefly on Mortality Statistics.—EMERSON and LARIMORE (*Arch. Int. Med.*, 1924, 34, 585) state that the increase in the incidence and death rate from diabetes in the United States, and in New York City in particular, has been more rapid than that of any other disease for which we have records in the last fifty years. This increase, while it has affected all ages to some degree, has been most marked among women at all ages and among both men and women over thirty-five years of age in particular. There are wide variations in the susceptibility to diabetes, or at least in their ability to survive when it develops in them, among persons of different races, those of Semitic stock showing consistently the highest death rates and those of the Negro race in the United States the lowest. It is not at all clear that these marked differences in the death rates from diabetes in the people of various races are of fundamental biologic significance, since many elements of occupation, economic status, dietetic habits, and so forth, may be found sufficient to explain the range of experience with what may fairly be considered a disease of a fatigued function in the great majority of cases. Although the relative rarity of diabetes among rural workers and those engaged in hard manual labor or trades would appear significant, the lack of a thoroughly satisfactory basis for calculating death rates by occupational groups in this country deprives the contrasting picture, of high rates among desk workers and others engaged chiefly in mental rather than physical processes for their living, of much of its force. Seasonal variations in death rates, calculated on a monthly basis, are marked and apparently significant. Whether temperature and other accompanying weather conditions are responsible, or the similar seasonal incidence of infections, usually accompanied by fever and interference with nutrition and deteriorated bodily resistance, cannot be stated on the basis of present information. Geographical distribution of the disease as measured by death rates in the United States appears to be explicable on the basis of differences in the age grouping, race, economic status, and occupation of the people, high rates being found where there is a

high proportion of the population in the later decades of life, after forty-five, where there are many Jews and where per capita wealth is high. Where life expectancy is high, there is a lower diabetes death rates than in states where life expectancy is low, but this is probable due to the fact that the low expectancy states are those with a high proportion of Negroes in the population. The changes in food habits in the United States have probably contributed to the increase of diabetes, the higher carbohydrate element and greater abundance or super-alimentation being believed to be a cause of overfatiguing the function of sugar tolerance. It is considered of much importance that educational measures be instituted to inform the public through medical and public health channels of the seriousness of the situation, and of the necessity of adjustment of food intake to exercise and *vice versa*. Moderation in the use of food and sufficient exercise with the entire body to justify the food absorbed, are important rules of hygiene for other reasons besides that of the relationship between obesity and diabetes, but if there were no other excuse for bringing this ancient teaching to people's attention, the greatly increased frequency of diabetes as a cause of sickness and death would alone seem to justify physicians and all those dealing with health and its protection in initiating and pushing vigorously a campaign of information in this subject.

The Seasonal Prevalence of Infantile Paralysis. Seasonal Variation in Case Fatality Rate.—AYCOCK and EATON (*Am. Jour. Hyg.*, 1924, 4, 681) state that there is a marked seasonal variation in the ratio of reported morbidity to reported mortality of infantile paralysis. This variation, in their opinion, is due largely to failure to recognize the milder forms of the disease in its "off season" and to a lesser extent to delayed reporting of cases as against prompt reporting of deaths. According to a calculated seasonal morbidity on the basis of the observations, infantile paralysis, although preponderantly a summer disease, prevails to a greater extent in the season from December to May than is shown by the reporting of cases. A calculated morbidity for 1921 also shows a secondary increase in the prevalence of the disease in March, which was not shown in the reporting of cases.

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